Edwards Lifesciences

Edwards SAPIEN
Transcatheter Heart Valve with the RetroFlex 3 Delivery System

Instructions for Use

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

Transfemoral Retrograde Approach

Implantation of the transcatheter heart valve should be performed only by physicians who have received Edwards Lifesciences training. The implanting physician should be experienced in balloon aortic valvuloplasty.

Please verify that you have the latest version of the instructions for use prior to using the device by visiting http://THVIFU.edwards.com or by calling 1.800.822.9837. In order to access the instructions for use, an IFU Code will be required.

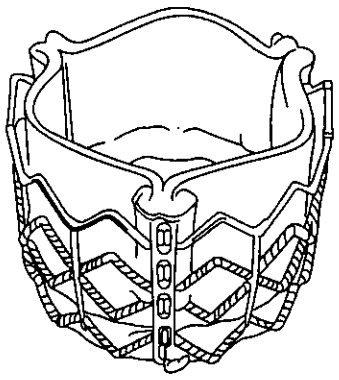
STERILE: The bioprosthesis is supplied sterilized with glutaraldehyde solution. The delivery system is supplied sterilized with ethylene oxide gas.

1.0 Device Description

- Edwards SAPIEN Transcatheter Heart Valve – Model 9000TFX (Figure 1)

The Edwards SAPIEN transcatheter heart valve (bioprosthesis) is comprised of a balloon-expandable, radiopaque, stainless steel (316 L) frame, three bovine pericardial tissue leaflets, and a polyethylene terephthalate (PET) fabric. The bioprosthesis is treated according to the Carpentier-Edwards ThermaFix process, packaged, and terminally sterilized in glutaraldehyde.

Figure 1. Edwards SAPIEN Transcatheter Heart Valve THV01



Bioprosthesis Diameter	Frame Height (Profile)
23 mm	14.3 mm
26 mm	16.1 mm

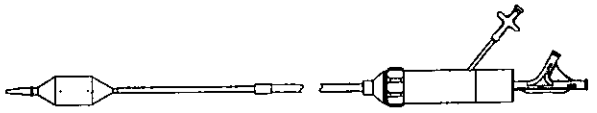
The following table identifies the bioprosthesis size that should be used based on native valve annulus size, as measured by transesophageal echocardiography (TEE).

Native Valve Annulus Size (Tissue Annulus Diameter)	Bioprosthesis Diameter
18-22 mm	23 mm
21-25 mm	26 mm

- RetroFlex 3 Delivery System – Model 9120FS23 for 23 mm valve procedure and 9120FS26 for 26 mm valve procedure (Figure 2)

The RetroFlex 3 delivery system includes a rotating wheel within the handle for articulation of the flex catheter, a tapered tip at the distal end of the delivery system to facilitate crossing the native valve, a balloon for deployment of the bioprosthesis, and radiopaque markers as indicated in Figure 2.

Figure 2. RetroFlex 3 Delivery System THV112



Black dots indicate position of radiopaque markers.

Nominal Balloon Diameter	RBP
23 mm	7 ATM (709 kPa)
26 mm	7 ATM (709 kPa)

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The following table identifies the access vessel diameters that should be used for delivery system access.

Ilio-Femoral Vessel Diameter	Delivery System
≥ 7 mm	23 mm
≥ 8 mm	26 mm

2.0 Indications

The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23 mm and 26 mm, is indicated for transfemoral delivery in patients with severe symptomatic calcified native aortic valve stenosis without severe aortic insufficiency and with ejection fraction > 20% who have been examined by a heart team including an experienced cardiac surgeon and a cardiologist and found to either be: 1) inoperable and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis; or 2) be operative candidates for aortic valve replacement but who have a Society of Thoracic Surgeons predicted operative risk score ≥ 8% or are judged by the heart team to be at a ≥ 15% risk of mortality for surgical aortic valve replacement.

The RetroFlex 3 Delivery System is indicated for the transfemoral delivery of the Edwards SAPIEN transcatheter heart valve.

3.0 Contraindications

The bioprosthesis and delivery system are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

4.0 Warnings

- Observation of the pacing lead throughout the procedure is essential to avoid the potential risk of pacing lead perforation.
- There is an increased risk of stroke in transcatheter aortic valve replacement procedures, as compared to balloon aortic valvuloplasty or other standard treatments.
- The devices are designed, intended, and distributed for single use only. **Do not re-sterilize or reuse the devices.** There are no data to support the sterility, non-pyrogenicity, and functionality of the devices after reprocessing.
- Incorrect sizing of the bioprosthesis may lead to paravalvular leak, migration, embolization and/or annular rupture.
- Accelerated deterioration of the bioprosthesis may occur in patients with an altered calcium metabolism. Bioprosthesis must remain hydrated at all times and cannot be exposed to solutions other than its shipping storage solution and sterile physiologic rinsing solution. Bioprosthesis leaflets mishandled or damaged during any part of the procedure will require replacement of the bioprosthesis.
- Caution should be exercised in implanting a bioprosthesis in patients with clinically significant coronary artery disease.
- Patients with pre-existing mitral valve devices should be carefully assessed prior to implantation of the bioprosthesis to ensure proper bioprosthesis positioning and deployment.
- Patients presenting with combination AV low flow, low gradient should undergo additional evaluation to establish the degree of aortic stenosis.
- Do not use the bioprosthesis if the tamper evident seal is broken, the storage solution does not completely cover the bioprosthesis, the temperature indicator has been activated, the bioprosthesis is damaged, or the expiration date has elapsed.
- Do not mishandle the RetroFlex 3 delivery system or use it if the packaging or any components are not sterile, have been opened or are damaged (e.g. kinked or stretched), or the expiration date has elapsed.
- Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.
- Patient injury could occur if the delivery system is not un-flexed prior to removal.
- Care should be exercised in patients with hypersensitivities to chromium, nickel, molybdenum, manganese, copper, silicon, and/or polymeric materials.
- The procedure should be conducted under fluoroscopic guidance. Some fluoroscopically guided procedures are associated with a risk of radiation injury to the skin. These injuries may be painful, disfiguring, and long-lasting.

5.0 Precautions

- Long-term durability has not been established for the bioprosthesis. Regular medical follow-up is advised to evaluate bioprosthesis performance.
- Glutaraldehyde may cause irritation of the skin, eyes, nose and throat. Avoid prolonged or repeated exposure to, or breathing of, the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, refer to Material Safety Data Sheet available from Edwards Lifesciences.
- To maintain proper valve leaflet coaptation, do not overinflate the deployment balloon.
- Appropriate antibiotic prophylaxis is recommended post-procedure in patients at risk for prosthetic valve infection and endocarditis.
- Bioprosthetic valve recipients should be maintained on anticoagulant and antiplatelet therapy (e.g. clopidogrel or ticlopidine [75 mg/day]) for 6 months post procedure and aspirin (75-100 mg/day) for life, except when contraindicated, as determined by their physician.
- The safety of the bioprosthesis implantation has not been established in patients who have:
  - Pre-existing prosthetic heart valve or valve repair device in any position
  - Severe ventricular dysfunction with ejection fraction < 20%
  - Hypertrophic cardiomyopathy with or without obstruction (HOCM)
- Safety, effectiveness, and durability have not been established for valve-in-valve procedures.
- Safety and effectiveness have not been established for patients with the following characteristics/comorbidities:
  - Non-calcified aortic annulus

- Congenital unicuspid or congenital bicuspid aortic valve
- Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation > 3+)
- Pre-existing prosthetic heart valve or prosthetic ring in any position
- Severe mitral annular calcification (MAC), severe (> 3+) mitral insufficiency, or Gorlin syndrome
- Blood dyscrasias defined as: leukopenia (WBC < 3000 mm^3), acute anemia (Hb < 9 mg%), thrombocytopenia (platelet count < 50,000 cells/mm^3), or history of bleeding diathesis or coagulopathy
- Hypertrophic cardiomyopathy with or without obstruction (HOCM)
- Echocardiographic evidence of intracardiac mass, thrombus, or vegetation
- A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media, which cannot be adequately premedicated
- Native aortic annulus size < 18 mm or > 25 mm as measured by echocardiogram
- Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5 cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding, or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe "unfolding" and tortuosity of the thoracic aorta
- Iliofemoral vessel characteristics that would preclude safe placement of 22F or 24F introducer sheath such as severe obstructive calcification, severe tortuosity or vessels size less than 7 mm in diameter
- Bulky calcified aortic valve leaflets in close proximity to coronary ostia

6.0 Potential Adverse Events

- Potential risks associated with the overall procedure including potential access complications associated with standard cardiac catheterization for the transfemoral access procedure, balloon valvuloplasty, the potential risks of conscious sedation and/or general anesthesia, and the use of angiography:
  - Death
  - Stroke/transient ischemic attack clusters or neurological deficit
  - Paralysis
  - Permanent disability
  - Respiratory insufficiency or respiratory failure
  - Hemorrhage requiring transfusion or intervention
  - Infundibulum injury
  - Cardiovascular injury including perforation or dissection of vessels, ventricle, myocardium or valvular structures that may require intervention
  - Annular tear or rupture
  - Pericardial effusion or cardiac tamponade
  - Embolization including air, calcific valve material or thrombus
  - Thrombus formation, plaque dislodgement, and embolization that may result in myocardial infarction, stroke, distal peripheral occlusion and/or death
  - Infection including septicemia and endocarditis
  - Heart failure
  - Myocardial infarction
  - Valve leaflet dehiscence
  - Renal insufficiency or renal failure
  - Conduction system injury (defect) which may require a permanent pacemaker
  - Arrhythmia
  - Retroperitoneal bleed
  - Femoral AV fistula or pseudoaneurysm
  - Reoperation
  - Peripheral ischemia or nerve injury
  - Restenosis
  - Pulmonary edema
  - Pleural effusion
  - Bleeding
  - Balloon rupture
  - Balloon separation following balloon rupture
  - Anemia
  - Abnormal lab values (including electrolyte imbalance)
  - Hypertension or hypotension
  - Allergic reaction to anesthesia or to contrast media
  - Hematoma
  - Syncope
  - Pain or changes at the access site
  - Exercise intolerance or weakness
  - Inflammation
  - Angina
  - Heart murmur
  - Fever
  - Mechanical failure of delivery system and/or accessories
  - Valvular tearing or trauma
- Additional potential risks specifically associated with the use of the bioprosthesis include, but may not be limited to the following:
  - Cardiac arrest
  - Cardiogenic shock
  - Emergency cardiac surgery
  - Cardiac failure or low cardiac output

- Coronary flow obstruction/transvalvular flow disturbance
- Device thrombosis requiring intervention
- Valve thrombosis
- Device embolization
- Device migration or malposition requiring intervention
- Valve deployment in unintended location
- Valve stenosis
- Structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflets retraction, stent creep, suture line disruption of components of a prosthetic valve, thickening, stenosis)
- Device degeneration
- Paravalvular or transvalvular leak
- Valve regurgitation
- Hemolysis
- Device explants
- Nonstructural dysfunction
- Non-emergent reoperation

All listed risks may include symptoms associated with the above mentioned medical conditions.

7.0 Directions for Use

7.1 Required Equipment

- Edwards SAPIEN Transcatheter Heart Valve
- Accessories required for the transcatheter aortic valve replacement procedure:
  - RetroFlex 3 Delivery System
  - 20 mm and/or 23 mm balloon catheter such as: RetroFlex Balloon Catheter Model 9120BC20 or Edwards Transfemoral Balloon Catheter Model 9350BC20 for use prior to 23 mm valve implantation and RetroFlex Balloon Catheter Model 9120BC23 or Edwards Transfemoral Balloon Catheter Model 9350BC23 for use prior to 26 mm valve implantation
  - RetroFlex 3 Introducer Sheath Set Model 9120S23 for 23 mm valve procedure and Model 9120S26 for 26 mm valve procedure
  - RetroFlex Dilator Kit Model 9100DKS7
  - Crimper Model 9100CR23 for 23 mm valve procedure and Model 9100CR26 for 26 mm valve procedure
  - Inflation device provided by Edwards Lifesciences for this application
- Standard cardiac catheterization lab equipment
- Fluoroscopy (fixed, mobile or semi-mobile fluoroscopy systems appropriate for use in percutaneous coronary interventions)
- Transesophageal or transthoracic echocardiography capabilities
- Exchange length 0.035 inch (0.89 mm) extra-stiff guidewire
- Temporary pacemaker (PM) and pacing lead
- Sterile rinsing basins, physiological saline, heparinized saline, and 15% diluted radiopaque contrast medium
- 20 cc or larger luer-lock syringe
- 60 cc or larger luer-lock syringe
- High-pressure 3-way stopcock

7.2 Bioprosthesis Handling and Preparation

Follow sterile technique during device preparation and implantation.

7.2.1 Bioprosthesis Rinsing Procedure

The bioprosthesis is packaged sterile in a plastic jar with a screw-cap closure and seal. Before opening, carefully examine the jar for evidence of damage (e.g., a cracked jar or lid, leakage, or broken or missing seals).

CAUTION: Bioprosthetic valves from containers found to be damaged, leaking, without adequate sterilant, or missing intact seals must not be used for implantation.

Step	Procedure
1	Set up two (2) sterile bowls with at least 500 mL of sterile physiological saline to thoroughly rinse the glutaraldehyde sterilant from the bioprosthesis.
2	The bioprosthesis is contained in the jar within a holder. Carefully remove the bioprosthesis/holder assembly from the jar without touching the tissue. The holder is tagged with the bioprosthesis' serial identification number. Inspect the bioprosthesis for any signs of damage to the frame or tissue.
3	Rinse the bioprosthesis as follows: Place the bioprosthesis in the first bowl of sterile, physiological saline. Be sure the saline solution completely covers the bioprosthesis and holder. With the bioprosthesis and holder submerged, slowly agitate (to **gently** swirl the bioprosthesis and holder) back and forth for a minimum of 1 minute. Transfer the bioprosthesis and holder to the second rinsing bowl of physiological saline and gently agitate for at least one more minute. Ensure the rinse solution in the first bowl is not used. The bioprosthesis should be left in the final rinse solution until needed to prevent the tissue from drying. **CAUTION: Do not allow the bioprosthesis to come in contact with the bottom or sides of the rinse bowl during agitation or swirling of the bioprosthesis. Care must be taken to ensure that the identification tag does not come in contact with the tissue and damage it. No other objects should be placed in the rinse bowls. The bioprosthesis should be kept hydrated throughout the rest of the preparation procedure to prevent the tissue from drying.**

7.2.2 Prepare Transfemoral Procedure Components

Step	Procedure
1	Refer to RetroFlex Dilator Kit, RetroFlex 3 Introducer Sheath Set and Crimper instructions for use on device preparation and handling.

Step	Procedure
2	Prime and flush the guidewire lumen of the delivery system with heparinized saline.
3	Insert an extra-stiff guidewire [0.035 inch (0.89 mm) and ≥ 150 cm long] in the guidewire lumen, leaving a 2 to 3 cm segment of the guidewire protruding from the distal tip.
4	Flush the delivery system with heparinized saline through the flush port.
5	Place the loader cap onto the delivery system, ensuring that the inside of the loader cap is in the same direction as the tapered tip.
6	Prepare a 60 mL or larger luer-lock syringe with diluted contrast medium (15:85 contrast to heparinized saline) and attach it to a 3-way stopcock on the balloon inflation port.
7	Completely fill the inflation device provided by Edwards Lifesciences and attach to 3-way stopcock. Ensure there are no air bubbles in the balloon. If an air bubble is detected, eliminate it while deflating the balloon. Close the stopcock to the syringe.
8	Insert the balloon into the balloon gauge located on the crimper. Inflate the balloon and verify its diameter fits the gauge with minimal friction. While gently pulling and pushing the balloon, verify that the balloon moves with some resistance within the gauge. If the balloon does not reach the correct diameter when fully inflated, add or discard some of the inflating solution in the inflation device provided by Edwards Lifesciences until the correct diameter is reached. The inflation device must remain connected to the delivery system throughout the rest of the procedure. **Note:** Correct balloon sizing is critical to successful valve deployment and valve function.
9	Close stopcock to the delivery system and remove any remaining contrast solution in inflation device provided by Edwards Lifesciences. Lock the inflation device.
10	Close the stopcock to the 60 mL syringe and verify the balloon is sized appropriately with the gauge. Remove the syringe. Unlock inflation device provided by Edwards Lifesciences and deflate the balloon while creating a three-wing fold configuration, and ensure no fluid is left behind. Lock the inflation device provided by Edwards Lifesciences.

7.2.3 Mount and Crimp the Bioprosthesis on the Delivery System

Step	Procedure
1	Remove the bioprosthesis from the holder and gently place the bioprosthesis into the crimper aperture.
2	Gradually crimp the bioprosthesis to a diameter of approximately 12 mm.
3	Remove the bioprosthesis from the crimper and place it on the delivery system with the inflow (fabric cuff end) of the bioprosthesis towards the distal end of the balloon catheter. Ensure that the inflow of the bioprosthesis is aligned with the proximal end of the tapered catheter tip.
4	Place the bioprosthesis back in the crimper aperture, and completely crimp until it fits inside the crimp gauge. **CAUTION: The physician must verify correct mounting/ orientation of the bioprosthesis prior to its implantation.**
5	Press on the balloon shoulders circumferentially to facilitate insertion into the flex catheter and loader.
6	Pull the proximal end of the balloon into the flex catheter until the proximal edge of the bioprosthesis is flush against the distal end of the flex catheter.
7	Flush the loader with sterile heparinized saline and insert the crimped bioprosthesis inside the loader.
8	Advance the bioprosthesis into the loader until the distal end of the delivery system tip is exposed.
9	Screw the loader cap to the loader, re-flush the flex catheter and close the stopcock to the delivery system. **Note:** Keep bioprosthesis hydrated until ready for implantation.
10	Remove guidewire and flush guidewire lumen.

7.3 Valvuloplasty and Bioprosthesis Delivery

Valvuloplasty and bioprosthesis delivery should be performed under conscious sedation and/or general anesthesia with hemodynamic monitoring in a catheterization lab/hybrid operating room with fluoroscopic and echocardiographic imaging capabilities.

Administer heparin to maintain the ACT at ≥ 250 sec.

CAUTION: Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.

CAUTION: Use of the retrograde approach may require a femoral artery cut-down with surgical closure of the puncture site due to the large size of the arteriotomy.

7.3.1 Baseline Parameters

Step	Procedure
1	Perform a supra-aortic angiogram with the projection of the native aortic valve perpendicular to the view.
2	Evaluate the height between the inferior aspect of the annulus and the inferior aspects of the lowest coronary ostium for subsequent prosthetic aortic valve implantation.
3	Introduce a pacemaker (PM) lead until its distal end is positioned in the right ventricle.
4	Set the stimulation parameters, and test pacing.

7.3.2 Valvuloplasty

Refer to the RetroFlex Balloon Catheter or the Edwards Transfemoral Balloon Catheter Instructions for Use (IFU) for information on device preparation and handling.

Note: Rapid ventricular pacing should be performed when using the RetroFlex Balloon Catheter or Edwards Transfemoral Balloon Catheter for valvuloplasty prior to aortic transcatheter valve implantation.

After placement of the balloon at the intended site, begin rapid ventricular pacing. Once the blood pressure has decreased to 50 mmHg or below, balloon inflation can commence.

CAUTION: Prosthetic valve implantation should not be carried out if the balloon cannot be fully inflated during valvuloplasty.

7.3.3 Bioprosthesis Delivery

Step	Procedure
1	Dilate the femoro-iliac vessel using the RetroFlex dilator kit. Refer to RetroFlex Dilator Kit IFU for information on device preparation and handling.
2	Insert the introducer sheath. Refer to the RetroFlex 3 Introducer Sheath Set IFU for additional information on device preparation and handling.
3	Insert the loader into the sheath.
4	Push the delivery system through the sheath. **CAUTION: The bioprosthesis should not be advanced through the sheath if the sheath tip is not past the aortic bifurcation.**
5	Retract loader to the proximal end of RetroFlex 3 delivery system.
6	The catheter articulates in a direction opposite from the flush port, and the flush port should be pointed away from the physician. Advance the RetroFlex 3 delivery system up the descending aorta; deflect the delivery system by rotating its handle "clockwise".
7	Cross the native aortic valve and position the bioprosthesis within the diseased valve.
8	Maintain the position of the bioprosthesis and retract the flex catheter, leaving the bioprosthesis in position. Verify that the flex catheter is completely off of the balloon before it is inflated and the bioprosthesis is deployed.
9	Position the mid-point of the bioprosthesis at the plane of the hinge points of the native valve leaflets.
10	Verify the correct location of the bioprosthesis with respect to the calcified valve.
11	Begin bioprosthesis deployment: • Unlock the inflation device. • Begin rapid pacing; once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. • Deploy the bioprosthesis by inflating the balloon with the entire volume in the inflation device. When the delivery system has been completely deflated, turn off the pacemaker. • De-articulate the delivery system and remove it from the sheath. **CAUTION: Patient injury could occur if the delivery system is not un-flexed prior to removal.**
12	Remove sheath when the ACT level is appropriate (e.g., reaches < 150 sec). Close puncture site.

8.0 How Supplied

STERILE: The bioprosthesis is supplied sterilized with glutaraldehyde solution. The delivery system is supplied sterilized with ethylene oxide gas.

8.1 Storage

The bioprosthesis must be stored between 10 °C-25 °C (50 °F-77 °F). Each jar is shipped in an enclosure containing a temperature indicator to detect exposure of the bioprosthesis to extreme temperature.

The RetroFlex 3 delivery system should be stored in a cool, dry place.

9.0 MR Safety

MR Conditional

Non-clinical testing has demonstrated that the Edwards SAPIEN THV (implant) is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 Tesla (T) or 3 Tesla.
- Spatial gradient field of 2500 Gauss/cm or less.
- Maximum whole-body-averaged specific absorption rate (SAR) of 2 W/kg for 15 minutes of scanning.
- Normal mode operation, as defined in IEC 60601-2-33 Ed. 3.0, of the MR system.

In non-clinical testing and analysis, the implant was determined to produce a temperature rise of less than 1.1 °C above background for a whole body SAR of 2.0 W/kg for 15 minutes of MR scanning in a 1.5 T cylindrical whole body MR system, assessed using a GE Signa whole body coil and a phantom designed to simulate human tissue. The phantom average SAR calculated using calorimetry was 2.2 W/kg and local background SAR at the site of the implant was 5.6 W/kg. The measured rise above background was 0.7 °C for a whole body SAR of 2 W/kg in a 3.0 T cylindrical bore whole body MR system, assessed using a GE Signa HDx whole body active shield MR scanner with software version 14/LX/MR and a phantom designed to simulate human tissue. The phantom average SAR calculated using calorimetry was 2.9 W/kg and local background SAR at the site of the implant was 8.4 W/kg.

The image artifact extended as far as 15 mm from the implant for spin echo images and 40 mm for gradient images when scanned in non-clinical testing in a 3.0 T GE Signa HDx MR system. The implant has not been evaluated in MR systems other than 1.5 or 3.0 T.

10.0 Patient Information

Patient education brochures are provided to each site and should be given to the patient to inform them of the risks and benefits of the procedure and alternatives in adequate time before the procedure to be read and discussed with their physician. A copy of this brochure may also be obtained from Edwards Lifesciences by calling 1.800.822.9837. A patient registration form is provided with each transcatheter heart valve. After implantation, all requested information should be completed on this form. The serial number may be found on the package and on the identification tag attached to the transcatheter heart valve. The original form should be returned to the

Edwards Lifesciences address indicated on the form and upon receipt, Edwards Lifesciences will provide an identification card to the patient.

11.0 Recovered Clinical Bioprosthesis

The explanted bioprosthesis should be placed into a suitable histological fixative such as 10% formalin or 2% glutaraldehyde and returned to the company. Refrigeration is not necessary under these circumstances. Contact Edwards Lifesciences to request an Explant Kit.

Disposal of Used Delivery Devices

Used delivery devices may be disposed of in the same manner that hospital waste and biohazardous materials are handled. There are no special risks related to the disposal of these devices.

12.0 Clinical Studies

The Placement of aortic transcatheter valves (PARTNER) trial, a prospective, randomized-controlled, multi-center pivotal trial, evaluated the safety and effectiveness of the Edwards SAPIEN transcatheter heart valve via transfemoral and transapical delivery in a stratified population of high-risk and inoperable patients with severe symptomatic native aortic stenosis. Patients were stratified into two cohorts based on their risk of operability for standard aortic valve replacement surgery – those who were considered high surgical risk were eligible for Cohort A, while inoperable patients were eligible for Cohort B due to coexisting conditions that resulted in the probability of death or irreversible morbidity exceeding 50%.

Study Design – Cohort A

This was a randomized study with the primary objective of ascertaining if TAVR is non-inferior to AVR surgery (7.5% margin) with respect to 12-month survival outcomes in high-risk surgical patients. Other objectives were focused on characterizing the benefit to risk ratio of TAVR relative to AVR.

Patients in Cohort A were first evaluated for vascular access to determine whether their peripheral arteries could accommodate the 22 or 24 French sheaths required for the transfemoral TAVR approach to deliver the 23 mm or 26 mm Edwards SAPIEN valve sizes. Those patients who could accommodate these sheaths were then randomized 1:1 between transfemoral TAVR and surgical AVR. Those patients whose arteries could not accommodate these sheaths were randomized 1:1 between transapical TAVR and surgical AVR.

The primary study endpoint was based on a pooled transapical and transfemoral analysis, and was defined as freedom from all cause mortality at one year for the high-risk cohort. All patients were followed for at least 1 year, and cross-over from the surgical AVR group to the TAVR group was not permitted, except when findings or events during the assigned procedure prevented the planned treatment. Clinically important endpoints included neurological adverse events, aortic regurgitation, bleeding, and vascular complications. In addition, the Sponsor prespecified secondary endpoints included the following: time from randomization to the first occurrence of a Major Adverse Cardiac and Cerebrovascular Event (MACCE) within one year for which MACCE definition was comprised of death, MI, stroke, and renal failure as defined by protocol, total hospital days through one year, NYHA functional class at one year, and 6-minute walk test at one year. Additional prespecified efficacy endpoints were measured at 30 days, six months, and one year for the following: functional improvement from baseline as measured per (1) NYHA functional classification, (2) EOA, and (3) 6-minute walk test, freedom from MACCE, improved Quality of Life (QoL), and improved valve function demonstrated by an improvement in EOA.

Study Design – Cohort B

This was a randomized study with the primary objective of ascertaining if TAVR is superior to standard therapy (including balloon aortic valvuloplasty) in a control group for inoperable patients with respect to 12-month survival outcomes. Other objectives were focused on characterizing the benefit to risk ratio of TAVR relative to the standard therapy control group.

Patients in Cohort B were also evaluated for vascular access and those meeting the criteria were randomized 1:1 to either transfemoral delivery of the Edwards SAPIEN valve or to a control group. Patients in the control group were treated with medication and/or balloon valvuloplasty. Patients in Cohort B who did not meet the criteria for vascular access were not eligible for the trial. The transapical procedure was not utilized in the study of these inoperable patients.

Study Results – Cohort A

A total of 699 (657 in the As-Treated [AT] population) high-risk patients with severe aortic stenosis were enrolled at 26 centers (23 in the United States) and assigned to TAVR (344 patients) or AVR (313 patients) with baseline characteristics described in Table 1. Among the TAVR patients, 240 were treated using transfemoral access and 104 were treated using transapical access. Severe aortic stenosis was defined as a mean gradient > 40 mmHg, jet velocity > 4.0 m per sec, or an initial aortic valve area (AVA) of 0.8 cm^2. The primary endpoint for the high-risk cohort was freedom from all cause mortality at one year. Clinical outcomes of TAVR (transfemoral and transapical) as compared to AVR are summarized in Tables 5, 6, and 7. There was a failure of attempt to treat 11% of the patients in the AVR arm and the inclusion of additional surgical procedures (such as coronary bypass grafting and operation to correct other valve lesions) in 13% of the AVR patients. The immediate conversion to surgical AVR in patients with failed TAVR occurred in 2.3% of the TAVR patients. The time from randomization to treatment in the TAVR arm was 10.6 days versus 15.6 days in the AVR arm ($P < 0.001$). At day 365, the Kaplan-Meier estimate of all cause death was 23.7% in the TAVR group, as compared to 25.2% in the AVR group. The estimated difference between these treatment groups is -1.5% with a one-sided lower 95% confidence interval for the difference of -4.0%, which is smaller than the pre-specified margin of -7.5%. The non-inferiority p-value for this difference is 0.0037, indicating that TAVR is non-inferior to AVR with respect to all cause death [Figure 3]. Pre-specified secondary endpoints included valve performance [Figures 6 and 7] and NYHA functional class [Figure 8]. When interpreting NYHA results, consider that the evaluation was unblinded. As with other heart valve trials, the patients are aware of their treatment group. Accordingly there is the potential for bias in the NYHA values, and there is no statistical method for estimating the bias. At 30 days, TAVR was more likely than AVR to reduce cardiac symptoms (New York Heart Association class ≤ II) ($P < 0.0030$). At 1 year, both TAVR and AVR improved cardiac symptoms with no evidence of treatment differences. The majority of strokes were reported at ≤ 30 days; the rate was 4.4% in the TAVR arm and 2.6% in the AVR arm ($P = 0.2064$). At one year, the rate of stroke was 5.8% in the TAVR arm and 3.0% in the AVR arm ($P = 0.0887$). At one year, the rate of mild aortic insufficiency was 50% in the TAVR arm and 18% in the AVR arm, the rate of moderate or greater aortic insufficiency was 23% in the TAVR arm and 3% in the AVR arm. Hemorrhagic/vascular events occurred in 24.5% of TAVR patients as compared to 27.8% of AVR patients between 0 and 30 days ($P = 0.3332$). Between 0 days and one year, hemorrhagic/vascular events occurred in 26.8% of TAVR patients as compared to 28.6% of AVR patients ($P = 0.6248$). Bleeding events occurred in 10.2% of TAVR patients vs. 28.4% of AVR patients ($P < 0.0001$) between 0 and 30 days and in 10.2% of TAVR patients vs. 28.4% of AVR patients between 0 and 365 days ($P < 0.0001$). Aortic valve gradients and areas improved significantly after TAVR and AVR at 30 days and 1 year. There were small

differences in aortic valve gradients and areas favoring TAVR (at 1 year, mean gradient 10.2 vs. 11.4 mmHg; P = 0.0131 and valve area 1.59 vs. 1.44 cm^2; P = 0.0027). Mild para-valvular regurgitation was more frequent after TAVR than AVR (at 30 days, 49% vs 7%, respectively with a P < 0.0001, at 1 year, 50% vs 9% P < 0.0001) and moderate or severe para-valvular regurgitation was also more frequent after TAVR than AVR (at 30-days, 11.7% vs. 0.9%, respectively, with P < 0.0001; at 1-year, 6.5% vs. 1.9%, respectively, with P < 0.0469). Mild and greater para-valvular regurgitation was found to be associated with late mortality. There were important differences in mortality outcomes for males and females comparing TAVR versus AVR therapies where males had similar 1 and 2 year mortality to AVR (28.5% and 25.2% at 1 year and 37.9% and 32.6% at 2 years respectively) and females had less frequent mortality with TAVR than AVR (18.5% and 29% at one year and 28.5% and 38.1% at 2 years respectively). Notably, baseline characteristics were different among males and females despite similar STS scores, where women were slightly older and were more frequently frail but males had a higher frequency of many important co-morbidities compared to the women, especially cardiovascular disease. This could explain the difference in 1 and 2 year mortality.

In patients with severe aortic stenosis who are at high-risk for operation, TAVR and AVR had similar survival after 1 year and similar improvement in cardiac symptoms. TAVR patients experienced a two times higher incidence of strokes and three times higher incidence of major vascular events. AVR patients experienced a two times higher incidence of bleeding. With respect to the transfemoral approach in both the ITT and AT populations, all cause mortality in the TAVR arm (22.2% and 21.4% respectively) was non-inferior to all cause mortality in the AVR arm (26.4% and 25.2% respectively) at 1 year. With respect to the transapical approach in both the ITT and AT populations, all cause mortality was higher in the TAVR arm (29.0% and 29.1% and 27.9% and 25.3% in the AVR respectively) at 1 year. The study was not powered for this analysis.

In conclusion, when used in the high surgical risk population mortality associated with TAVR is not inferior to the mortality associated with surgical AVR at one year, but has double the stroke rate, three times the vascular complication rate, but half the bleeding rate.

Study Results – Cohort B

A total of 358 patients (ITT population) with severe aortic stenosis were enrolled and underwent 1:1 randomization at 22 centers (18 in the United States) with baseline characteristics described in Table 2. Severe aortic stenosis was defined as an aortic-valve area of less than 0.8 cm^2, a mean aortic-valve gradient of 40 mmHg or more, or a peak aortic-jet velocity of 4.0 m per second or more. The primary end point was the rate of death from any cause over the duration of the trial. At 1 year, the rate of death from any cause (Kaplan-Meier analysis) was 30.7% with TAVR, as compared with 50.7% in the group not receiving the valve (hazard ratio with TAVR, 0.51; 95% confidence interval [CI], 0.39 to 0.68; P < 0.0001) (Figure 9). A total of 141 of the 179 (78.8%) patients in the control group underwent balloon aortic valvuloplasty (BAV). In addition, 11 patients (6.1%) underwent aortic valve replacement. 5 patients (2.8%) received an LV-descending aortic conduit, and 4 patients (2.2%) received a THV outside the US. The co-primary composite end point was time of death from any cause or the time to the first occurrence of repeat hospitalization. The rate of the composite end point of death from any cause or repeat hospitalization was 43.6% with TAVR as compared with 71.6% in the control group (hazard ratio, 0.45; 95% CI, 0.35 to 0.59; P < 0.0001) (Figure 10). Prespecified secondary end points included the rate of death from cardiovascular causes (Figure 11), NYHA functional class (Figure 14), valve performance (Figures 12 and 13), and the distance covered during a 6-minute walk test. Among survivors at 1 year, the rate of cardiac symptoms (New York Heart Association class III or IV) was lower among patients who had undergone TAVR than among those in the control group (23.9% vs. 60.8%, P < 0.001). When interpreting NYHA results, consider that the evaluation was unblinded. As with other heart valve trials, the patients are aware of their treatment group. Accordingly there is the potential for bias in the NYHA values, and there is no statistical method for estimating the bias. At 30 days, TAVR, as compared with the control, was associated with a higher incidence of strokes (7.3% vs. 1.7%, P = 0.02) and major vascular complications (16.8% vs. 1.1%, P < 0.0001). The time from index procedure to stroke in the TAVR group was as follows: 1 stroke at 12 days before the index procedure but after randomization, 4 strokes on the day of the index procedure, 2 strokes on the first post-operative day and 2 on the second post-operative day, and one stroke each on days 3, 5, 10, 23, 39, 51, 75, 120, 136, and 151. At 1 year, the rate of hemorrhagic vascular complication was 34.3% in the TAVR group, as compared to 17.7% in the control group. At 1 year, the rate of bleeding events was 17.3% in the TAVR group, as compared to 2.2% in the control group. Additionally, at 1 year, the rate of endocarditis was 1.4% in the TAVR group, as compared to 0.8% in the control group. Mean index hospital stay was 8.5 days for the TAVR group, as compared to 7.6 days for the control group. Mean days alive out of hospital was 273.8 days for the TAVR group and 210.2 days for the control group. At 1 year, the rate of aortic regurgitation for the TAVR group was as follows: 2% of patients at 4+, 13% of patients at 3+, 50% of patients at 2+, 20% of patients at 1+, and 11% of patients with no regurgitation. In comparison, the rate of aortic regurgitation of the control group was as follows: 17% of patients at 3+, 39% of patients at 2+, 37% of patients at 1+, and 7% of patients with no regurgitation.

Procedure data for the TAVR group is summarized in Table 4. Clinical outcomes of TAVR as compared with the control are summarized in Table 8. In the two years after TAVR, there was no deterioration in the functioning of the bioprosthetic valve, as assessed by evidence of stenosis or regurgitation on an echocardiogram.

Additional data for the inoperable patient population in Cohort B has been collected, reviewed, and adjudicated; results are summarized in Table 8.

In patients with severe aortic stenosis who were not suitable candidates for surgery, TAVR, as compared with the control, significantly reduced the rates of death from any cause, the composite end point of death from any cause or repeat hospitalization, and cardiac symptoms, despite the higher incidence of stroke and major vascular events.

These products are manufactured and sold under one or more of the following US patent(s): US Patent No. 5,411,552; 5,931,969; 6,210,957; 6,214,054; 6,547,827; 6,561,970; 6,908,481; 7,214,344; 7,510,575; 7,530,253; 7,585,321; 7,780,723; 8,057,540; and RE40570 and corresponding foreign patents. Additional patents are pending.

Table 1: COHORT A – Baseline Characteristics of the Patients and Echocardiographic Findings* (AT Population)							
	Transapical Approach		Transfemoral Approach		Pooled Approaches		P Value
Characteristic	AVR (N = 92)	TAVR (N = 104)	AVR (N = 221)	TAVR (N = 240)	AVR (N = 313)	TAVR (N = 344)	
Age – yr	83.4 ± 5.5	82.9 ± 7.0	84.8 ± 6.6	83.9 ± 6.8	84.4 ± 6.3	83.6 ± 6.8	0.12
Male sex – no. (%)	55 (59.8)	53 (51.0)	124 (56.1)	145 (60.4)	179 (57.2)	198 (57.6)	0.94
STS score†	12.01 ± 3.5	11.7 ± 3.6	11.5 ± 3.3	11.9 ± 3.2	11.7 ± 3.4	11.8 ± 3.3	0.65
NYHA class – no. (%):							
II	4/92 (4.3)	8/104 (7.7)	12/221 (5.4)	12/240 (5.0)	16/313 (5.1)	20/344 (5.8)	0.73
III or IV	88/92 (95.7)	96/104 (92.3)	209/221 (94.6)	228/240 (95.0)	297/313 (94.9)	324/344 (94.2)	> 0.999
Coronary artery disease – no. (%)	76/92 (82.6)	77/104 (74.0)	165/221 (74.7)	181/240 (75.4)	241/313 (77.0)	258/344 (75.0)	0.58
Previous myocardial infarction – no./total no. (%)	34/92 (37.0)	28/104 (26.9)	56/218 (25.7)	64/239 (26.8)	90/310 (29.0)	92/343 (26.8)	0.54
Previous intervention – no./total no. (%)							
CABG	51/92 (55.4)	51/104 (49.0)	88/221 (39.8)	95/240 (39.6)	139/313 (44.4)	146/344 (42.4)	0.64
PCI	39/91 (42.9)	33/104 (31.7)	62/221 (28.1)	82/238 (34.5)	101/312 (32.4)	115/342 (33.6)	0.74
Balloon aortic valvuloplasty	10/92 (10.9)	13/104 (12.5)	22/221 (10.0)	33/240 (13.8)	32/313 (10.2)	46/344 (13.4)	0.2287
Cerebral vascular disease – no./total no. (%)	26/86 (30.2)	40/96 (41.7)	53/206 (25.7)	56/227 (24.7)	79/292 (27.1)	96/323 (29.7)	0.48
Peripheral vascular disease – no./total no. (%)	56/90 (62.2)	65/103 (63.1)	76/217 (35.0)	83/238 (34.9)	132/307 (43.0)	148/341 (43.4)	0.94
COPD – no./total no. (%):							
Any	41/92 (44.6)	46/104 (44.2)	97/221 (43.9)	104/240 (43.3)	138/313 (44.1)	150/344 (43.6)	0.94
Oxygen-dependent	7/92 (7.6)	11/104 (10.6)	16/221 (7.2)	21/240 (8.8)	23/313 (7.3)	32/344 (9.3)	0.90
Creatinine > 2 mg/dL (177 µmol/liter) – no./total no. (%)	9/92 (9.8)	7/103 (6.8)	11/221 (5.0)	30/237 (12.7)	20/313 (6.4)	37/340 (10.9)	0.05
Atrial fibrillation – no./total no. (%)	17/33 (51.5)	31/58 (53.4)	51/121 (42.1)	49/138 (35.5)	68/154 (44.2)	80/196 (40.8)	0.59
Permanent pacemaker – no./total no. (%)	17/92 (18.5)	21/104 (20.2)	53/221 (24.0)	48/240 (20.0)	70/313 (22.4)	69/344 (20.1)	0.50
Pulmonary hypertension – no./total no. (%)	38/92 (41.3)	55/104 (52.9)	112/221 (50.7)	117/240 (48.8)	150/313 (47.9)	172/344 (50.0)	0.07
Extensively calcified aorta – no. (%)	1/92 (1.1)	2/104 (1.9)	1/221 (0.5)	0/240 (0.0)	2/313 (0.6)	2/344 (0.6)	> 0.999
Deleterious effects of chest-wall irradiation – no. (%)	0/92 (0.0)	2/104 (1.9)	2/221 (0.9)	1/240 (0.4)	2/313 (0.6)	3/344 (0.9)	> 0.999
Chest-wall deformity – no. (%)	1/92 (1.1)	0/104 (0.0)	0/221 (0.0)	0/240 (0.0)	1/313 (0.3)	0/344 (0.0)	0.48
Liver disease – no./total no. (%)	0/92 (0.0)	2/104 (1.9)	9/221 (4.1)	6/240 (2.5)	9/313 (2.9)	8/344 (2.3)	0.81
Echocardiographic findings							
Aortic-valve area – cm^2 (n, mean)	88, 0.7 ± 0.2	95, 0.7 ± 0.2	207, 0.6 ± 0.2	223, 0.7 ± 0.2	295, 0.6 ± 0.2	318, 0.7 ± 0.2	0.28
Mean aortic-valve gradient – mmHg (n, mean)	90, 40.5 ± 12.9	97, 41.7 ± 13.9	210, 44.6 ± 14.8	229, 43.0 ± 14.8	300, 43.4 ± 14.3	326, 42.6 ± 14.5	0.49
Mean LVEF – (n, mean)	89, 53.5 ± 10.9	98, 53.6 ± 12.2	211, 53.3 ± 13.3	232, 52.2 ± 14.0	300, 53.3 ± 12.6	330, 52.6 ± 13.5	0.48
Moderate or severe mitral regurgitation – no./total no. (%)¶	19/89 (21.3)	19/99 (19.2)	44/208 (21.2)	46/230 (20.0)	63/297 (21.2)	65/329 (19.8)	0.69

* Plus–minus values are means ± SD. To convert the value for creatinine to micromoles per liter, multiply by 88.4. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve replacement.

† The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher numbers indicating greater risk. An STS score higher than 10% indicates very high surgical risk.

¶ Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

Table 2: COHORT B – Baseline Characteristics of the Patients and Echocardiographic Findings* (ITT Population)			
Characteristic	**TAVR (N = 179)**	**Control Group (N = 179)**	**P Value**
Age – yr	83.1 ± 8.6	83.2 ± 8.3	0.95
Male sex – no. (%)	82 (45.8)	84 (46.9)	0.92
STS score†	11.2 ± 5.8	11.9 ± 4.8	0.14
NYHA class – no. (%):			0.68
II	14 (7.8)	11 (6.1)	
III or IV	165 (92.2)	168 (93.9)	
Coronary artery disease – no. (%)	121 (67.6)	133 (74.3)	0.20
Previous myocardial infarction – no./total no. (%)	33/177 (18.6)	47/179 (26.3)	0.10
Previous intervention – no./total no. (%)			
CABG	58/179 (32.4)	73/179 (40.8)	0.12
PCI	47/179 (26.3)	39/179 (21.8)	0.39
Balloon aortic valvuloplasty	25/154 (16.2)	39/160 (24.4)	0.09
Cerebral vascular disease – no./total no. (%)	48/175 (27.4)	46/171 (26.9)	1.00
Peripheral vascular disease – no./total no. (%)	55/178 (30.9)	45/179 (25.1)	0.24
COPD – no. (%):			
Any	74 (41.3)	94 (52.5)	0.04
Oxygen-dependent	38 (21.2)	46 (25.7)	0.38
Creatinine > 2 mg/dL (177 µmol/liter) – no./total no. (%)	8/179 (4.5)	16/178 (9.0)	0.10
Atrial fibrillation – no./total no. (%)	28/85 (32.9)	39/80 (48.8)	0.04
Permanent pacemaker – no./total no. (%)	35/179 (19.6)	31/179 (17.3)	0.68
Pulmonary hypertension – no./total no. (%)	50/118 (42.4)	53/121 (43.8)	0.90
Extensively calcified aorta – no. (%)	34 (19.0)	20 (11.2)	0.05
Deleterious effects of chest-wall irradiation – no. (%)	16 (8.9)	15 (8.4)	1.00
Chest-wall deformity – no. (%)	15 (8.4)	9 (5.0)	0.29
Liver disease – no./total no. (%)	6/177 (3.4)	6/178 (3.4)	1.00
Echocardiographic findings			
Aortic-valve area – cm^2	0.6 ± 0.2	0.6 ± 0.2	0.97
Mean aortic-valve gradient – mmHg	44.5 ± 15.7	43.0 ± 15.3	0.39
Mean LVEF – %	53.9 ± 13.1	51.1 ± 14.3	0.06
Moderate or severe mitral regurgitation – no./total no. (%)¶	38/171 (22.2)	38/165 (23.0)	0.90

* Plus–minus values are means ± SD. To convert the value for creatinine to micromoles per liter, multiply by 88.4. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve replacement.

† The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher numbers indicating greater risk. An STS score higher than 10% indicates very high surgical risk.

¶ Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

Table 3: COHORT A – Procedure Data (AT Population)			
	TA TAVR	TF TAVR	Pooled AVR
Variable	**Mean or % of patients (min-max)**		
Total time of procedure (min)	225 (93-595)	246 (84-624)	333 (70-750)
Skin to skin time (min)	114	142	230 (169-295)
Fluoroscopy time (min)	35	30	N/A
Volume of contrast (ml)	104	148	N/A
Use of CPB	8.8%	2.1%	100%
Use of general anesthesia	100%	100%	100%
# of devices used			
0	2.9%	4.6%	N/A
1	89.2%	90.8%	100%
2	6.9%	4.2%	N/A
3	1.0%	0.4%	N/A
Valve-in-valve procedure	1.0%	0.4%	N/A
Emergent operation due to device or procedure	1.0%	1.3%	3.8%
Valve Size			
19 mm	N/A	N/A	11.9%
21 mm	N/A	N/A	39.7%
22 mm	N/A	N/A	0.3%
23 mm	51.5%	46.8%	34.9%
25 mm	N/A	N/A	11.9%
26 mm	48.5%	53.3%	N/A
27 mm	N/A	N/A	1.0%
29 mm	N/A	N/A	0.3%
Adverse event during procedure	19.6%	21.3%	14.7%
Device malfunction	2.0%	1.3%	N/A
Device Success (deployment, AVA > 0.9, AI < 3+, 1 valve)	84.5%	80.4%	N/A
Procedure Success (Device success, no MACCE < 30d)	75.3%	76.0%	N/A

Table 4: COHORT B – TAVR Procedure Data	
Variable	**Mean or % of patients (min-max)**
Total time of procedure (min)	262 (139-616)
Skin to skin time (min)	150 (34-553)
Fluoroscopy time (min)	29 (10-68)
Volume of contrast (ml)	132 (10-450)
Use of CPB	1.1%
Use of general anesthesia	100%
# of devices used	
0	4.6%
1	89.1%
2	5.7%
3	0.6%
Valve-in-valve procedure	2.3%
Emergent operation due to device or procedure	1.1%
Valve Size	
23 mm	56.6%
26 mm	43.4%
Adverse event during procedure	39.4%
Device malfunction	3.4%
Device Success (deployment, AVA > 0.9, AI < 3+, 1 valve)	78.2%
Procedure Success (Device success, no MACCE < 30d)	71.8%

Table 5: COHORT A – Clinical Outcomes of the Pooled TAVR and Pooled AVR Groups up to 2 Years (AT Population)

	30 Days				31 Days-1 Year				1 Year-2 Years			
Outcome	Pooled TAVR (N = 344)	KM Event rate TAVR*	Pooled AVR (N = 313)	KM Event rate AVR	Pooled TAVR (N = 344)	KM Event rate TAVR*	Pooled AVR (N = 313)	KM Event rate AVR	Pooled TAVR (N = 344)	KM Event rate TAVR*	Pooled AVR (N = 313)	KM Event rate AVR
Death	18	5.2%	25	8.0%	63	23.7%	53	25.2%	33	33.9%	21	32.7%
Death from cardiovascular cause[a]	14	4.1%	9	2.9%	30	13.6%	24	11.5%	20	20.8%	16	18.5%
Repeat hospitalization[b]	18	5.4%	18	6.1%	40	17.3%	29	16.6%	15	23.8%	9	20.8%
Death from any cause or repeat hospitalization[b]	35	10.2%	43	13.8%	86	33.9%	74	35.5%	48	46.2%	33	44.4%
TIA[d]	3	0.9%	1	0.3%	5	2.7%	3	1.5%	2	3.6%	2	2.7%
All Stroke[c]	15	4.4%	8	2.6%	4	5.8%	1	3.0%	4	7.5%	3	4.4%
Myocardial Infarction[g]												
All	0	0.0%	1	0.3%	0	0.0%	0	0.3%	2	0.0%	0	1.3%
Peri-procedural	0	0.0%	1	0.3%	0	0.0%	0	0.3%	0	0.0%	0	0.3%
Aortic Insufficiency												
Mild	138	42.1%	34	11.9%	105	60.3%	18	16.4%	38	62.7%	8	17.8%
Moderate or greater	43	13.2%	4	1.4%	21	17.4%	4	2.7%	8	19.9%	1	2.7%
Hemorrhagic Vascular Complication[f]	84	24.5%	87	27.8%	10	26.8%	3	28.6%	3	28.0%	2	29.4%
Major Vascular Complication[i]	38	11.1%	12	3.8%	0	11.1%	0	3.8%	1	11.4%	0	3.8%
Renal Failure[h]	13	3.8%	14	4.6%	4	5.2%	5	6.5%	2	6.0%	0	6.5%
Renal Insufficiency	19	5.6%	18	5.8%	3	6.6%	7	7.8%	4	8.1%	1	8.3%
Bleeding Event[e]	35	10.2%	89	28.4%	0	10.2%	0	28.4%	0	10.2%	0	28.4%
Cardiac reintervention												
Balloon aortic valvuloplasty	0	N/A	0	N/A	2	N/A	0	N/A	0	N/A	0	N/A
Repeat TAVR	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Aortic-valve replacement	7	N/A	0	N/A	1	N/A	0	N/A	1	N/A	0	N/A
Endocarditis	0	0.0%	1	0.3%	3	1.0%	2	1.1%	1	1.5%	0	1.1%
New pacemaker	16	4.7%	14	4.6%	4	6.1%	2	5.3%	2	6.9%	3	6.8%

*Kaplan-Meier event rates are reported at 30 days, one year, and two years.

N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.

Data presented as n (%) of patients unless otherwise specified.

a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.

b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).

c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.

d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.

e. Bleeding event is defined as ≥ 2 units within the index procedure.

f. Hemorrhagic vascular complications are defined as a hematoma at the access site > 5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index procedure was reported as a serious adverse event.

g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non-Q-wave MI.

h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).

i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.

Table 6: COHORT A – Clinical Outcomes in the Transfemoral Group up to 2 Years (AT Population)												
	30 Days				31 Days-1 Year				1 Year-2 Years			
Outcome	TF TAVR (N = 240)	KM Event rate TAVR*	AVR (N = 221)	KM Event rate AVR	TF TAVR (N = 240)	KM Event rate TAVR*	AVR (N = 221)	KM Event rate AVR	TF TAVR (N = 240)	KM Event rate TAVR*	AVR (N = 221)	KM Event rate AVR
Death	9	3.7%	18	8.2%	42	21.4%	37	25.2%	21	30.7%	13	31.6%
Death from cardiovascular cause[a]	8	3.3%	7	3.2%	19	12.0%	17	11.8%	14	19.0%	9	17.3%
Repeat hospitalization[b]	13	5.5%	12	5.8%	29	17.6%	22	17.3%	8	22.4%	4	19.8%
Death from any cause or repeat hospitalization[b]	21	8.7%	30	13.6%	59	31.8%	52	35.3%	31	42.2%	18	42.2%
TIA[d]	3	1.3%	0	0.0%	2	2.3%	1	0.6%	1	2.8%	1	1.4%
All Stroke[c]	8	3.3%	3	1.4%	1	3.8%	0	1.4%	2	5.0%	1	2.0%
Myocardial Infarction[g]												
All	0	0.0%	1	0.5%	0	0.0%	0	0.5%	0	0.0%	1	1.1%
Peri-procedural	0	0.0%	1	0.5%	0	0.0%	0	0.5%	0	0.0%	0	0.5%
Aortic Insufficiency												
Mild	105	45.5%	24	11.9%	84	65.9%	12	16.3%	32	68.2%	5	17.3%
Moderate or greater	38	16.5%	2	1.0%	19	21.8%	3	2.8%	7	25.1%	1	2.8%
Hemorrhagic Vascular Complication[f]	69	28.8%	61	27.6%	5	30.2%	2	28.7%	1	30.7%	2	29.8%
Major Vascular Complication[i]	34	14.2%	7	3.2%	0	14.2%	0	3.2%	1	14.7%	0	3.2%
Renal Failure[h]	8	3.4%	7	3.2%	3	4.7%	4	5.5%	2	5.8%	0	5.5%
Renal Insufficiency	7	2.9%	13	6.0%	2	3.9%	6	8.2%	4	5.9%	0	8.2%
Bleeding Event[e]	27	11.3%	63	28.5%	0	11.3%	0	28.5%	0	11.3%	0	28.5%
Cardiac reintervention												
Balloon aortic valvuloplasty	0	N/A	0	N/A	2	N/A	0	N/A	0	N/A	0	N/A
Repeat TAVR	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Aortic-valve replacement	4	N/A	0	N/A	1	N/A	0	N/A	1	N/A	0	N/A
Endocarditis	0	0.0%	0	0.0%	2	1.0%	2	1.1%	1	1.6%	0	1.1%
New pacemaker	11	4.6%	9	4.2%	3	6.0%	0	4.2%	2	7.2%	3	6.2%

*Kaplan-Meier event rates are reported at 30 days, one year, and two years.

N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.

Data presented as n (%) of patients unless otherwise specified.

a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.

b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).

c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.

d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.

e. Bleeding event is defined as ≥ 2 units within the index procedure.

f. Hemorrhagic vascular complications are defined as a hematoma at the access site > 5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index procedure was reported as a serious adverse event.

g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non-Q-wave MI.

h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).

i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.

Table 7: COHORT A – Clinical Outcomes in the Transapical Group up to 2 Years (AT Population)												
	30 Days				31 Days-1 Year				1 Year-2 Years			
Outcome	TA TAVR (N = 104)	KM Event rate TAVR*	AVR (N = 92)	KM Event rate AVR	TA TAVR (N = 104)	KM Event rate TAVR*	AVR (N = 92)	KM Event rate AVR	TA TAVR (N = 104)	KM Event rate TAVR*	AVR (N = 92)	KM Event rate AVR
Death	9	8.7%	7	7.6%	21	29.1%	16	25.3%	12	41.3%	8	35.5%
Death from cardiovascular cause[a]	6	5.8%	2	2.2%	11	17.4%	7	10.8%	6	25.2%	7	21.6%
Repeat hospitalization[b]	5	5.1%	6	6.8%	11	16.7%	7	14.9%	7	27.4%	5	23.3%
Death from any cause or repeat hospitalization[b]	14	13.5%	13	14.1%	27	38.7%	22	36.3%	17	55.3%	15	49.6%
TIA[d]	0	0.0%	1	1.1%	3	3.7%	2	3.9%	1	5.8%	1	5.6%
All Stroke[c]	7	7.0%	5	5.5%	3	10.8%	1	7.0%	2	13.8%	2	10.0%
Myocardial Infarction[g]												
All	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.5%
Peri-procedural	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Aortic Insufficiency												
Mild	33	34.0%	10	11.8%	21	45.8%	6	16.4%	6	48.1%	3	19.4%
Moderate or greater	5	5.3%	2	2.4%	2	6.6%	1	2.4%	1	6.6%	0	2.4%
Hemorrhagic Vascular Complication[f]	15	14.5%	26	28.3%	5	19.2%	1	28.3%	2	22.0%	0	28.3%
Major Vascular Complication[i]	4	3.9%	5	5.4%	0	3.9%	0	5.4%	0	3.9%	0	5.4%
Renal Failure[h]	5	5.0%	7	7.7%	1	6.2%	1	8.9%	0	6.2%	0	8.9%
Renal Insufficiency	12	11.9%	5	5.5%	1	13.1%	1	6.9%	0	13.1%	1	8.4%
Bleeding Event[e]	8	7.7%	26	28.3%	0	7.7%	0	28.3%	0	7.7%	0	28.3%
Cardiac reintervention												
Balloon aortic valvuloplasty	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Repeat TAVR	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Aortic-valve replacement	3	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Endocarditis	0	0.0%	1	1.1%	1	1.2%	0	1.1%	0	1.2%	0	1.1%
New pacemaker	5	5.0%	5	5.6%	1	6.2%	2	8.1%	0	6.2%	0	8.1%

*Kaplan-Meier event rates are reported at 30 days, one year, and two years.
N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.
Data presented as n (%) of patients unless otherwise specified.
a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.
d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.
e. Bleeding event is defined as ≥ 2 units within the index procedure.
f. Hemorrhagic vascular complications are defined as a hematoma at the access site > 5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index procedure was reported as a serious adverse event.
g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non-Q-wave MI.
h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).
i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.

Table 8: COHORT B – Clinical Outcomes up to 2 Years (ITT Population)												
	30 Days				31 Days-1 Year				1 Year-2 Years			
Outcome	TAVR (N = 179)	KM Event rate*	Control Group (N = 179)	KM Event rate	TAVR (N = 179)	KM Event rate*	Control Group (N = 179)	KM Event rate	TAVR (N = 179)	KM Event rate*	Control Group (N = 179)	KM Event rate
Death from any cause	9	5.0%	5	2.8%	46	30.7%	84	50.7%	22	43.3%	28	68.0%
Death from cardiovascular cause[a]	8	4.5%	3	1.7%	27	20.5%	72	44.6%	15	31.0%	25	62.4%
Repeat hospitalization[b]	12	6.9%	18	10.2%	35	27.0%	70	53.9%	15	35.0%	24	72.5%
Death from any cause or repeat hospitalization[b]	21	11.7%	22	12.3%	62	44.1%	117	71.6%	31	56.7%	45	87.9%
TIA[d]	0	0.0%	0	0.0%	1	0.7%	0	0.0%	2	2.5%	0	0.0%
All Stroke[c]	13	7.3%	3	1.7%	6	11.2%	5	5.5%	3	13.8%	0	5.5%
Myocardial Infarction[g]												
All	0	0.0%	0	0.0%	1	0.8%	1	0.7%	1	1.6%	1	2.5%
Peri-procedural	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Aortic Insufficiency												
Mild	89	53.3%	59	34.1%	49	66.2%	21	47.3%	24	70.7%	9	49.6%
Moderate or greater	23	13.9%	21	12.1%	15	19.4%	9	16.8%	4	22.0%	3	19.0%
Hemorrhagic Vascular Complication[f]	46	25.8%	10	5.7%	16	34.3%	16	17.7%	8	39.8%	5	22.9%
Major Vascular Complication[i]	30	16.8%	2	1.1%	2	17.4%	2	2.8%	0	17.4%	0	2.8%
Renal Failure[h]	2	1.1%	3	1.7%	2	2.3%	4	4.7%	1	3.2%	3	7.6%
Renal Insufficiency	8	4.6%	1	0.6%	4	7.3%	5	4.2%	3	9.9%	4	9.6%
Bleeding Events[e]	29	16.2%	4	2.2%	2	17.3%	0	2.2%	0	17.3%	0	2.2%
Cardiac reintervention												
Balloon aortic valvuloplasty	3	1.7%	11	6.1%	0	1.7%	41	29.1%	2	3.4%	7	33.0%
Repeat TAVR[e]	3	N/A	N/A	N/A	0	N/A	N/A	N/A	0	N/A	N/A	N/A
Aortic-valve replacement	0	0.0%	4	2.3%	0	0.0%	6	7.6%	1	0.9%	1	8.9%
Endocarditis	0	0.0%	0	0.0%	2	1.4%	1	0.8%	1	2.3%	0	0.8%
New pacemaker	6	3.4%	9	5.1%	2	4.7%	5	8.6%	2	6.4%	0	8.6%

*Kaplan-Meier event rates are reported at 30 days, one year, and two years.
N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.
Data presented as n (%) of patients unless otherwise specified.
a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.
d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.
e. Bleeding event is defined as ≥ 2 units within the index procedure.
f. Hemorrhagic vascular complications are defined as a hematoma at the access site > 5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index procedure was reported as a serious adverse event.
g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non-Q-wave MI.
h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).
i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.

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Figure 3. COHORT A - Primary Endpoint:
All Cause Mortality (AT Population)
(68% confidence limits displayed)

THV269

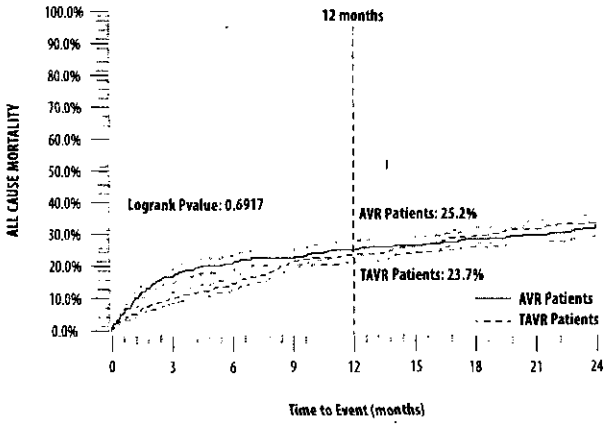


Figure 4. COHORT A - Secondary Endpoint:
Mortality or Repeat Hospitalization (AT Population)
(68% confidence limits displayed)

THV270

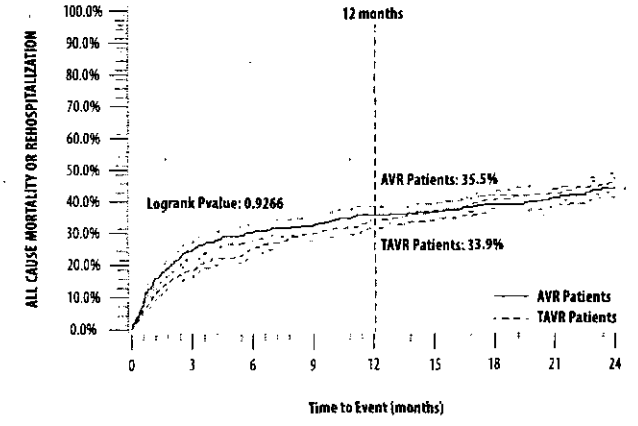


Figure 5. COHORT A - Secondary Endpoint:
Death from Cardiovascular Cause (AT Population)
(68% confidence limits displayed)

THV271

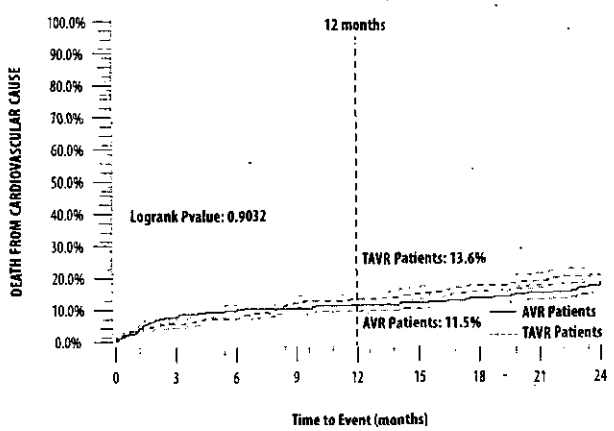


Figure 6. COHORT A - Secondary Endpoint:
AVA Over Time (AT Population)
(one standard deviation displayed)

THV272

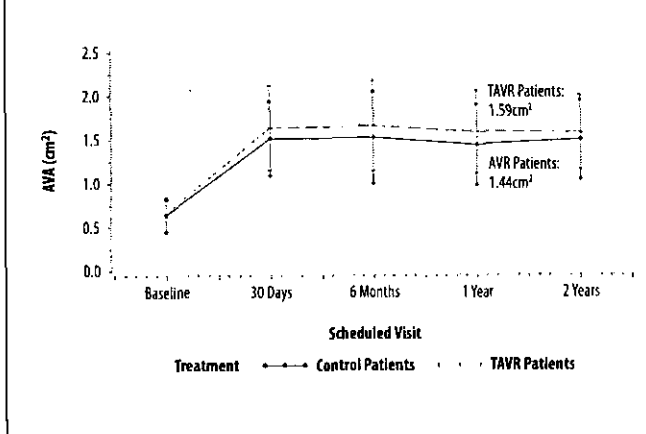


Figure 7. COHORT A - Secondary Endpoint:
Mean Gradient Over Time (AT Population)
(one standard deviation displayed)

THV273

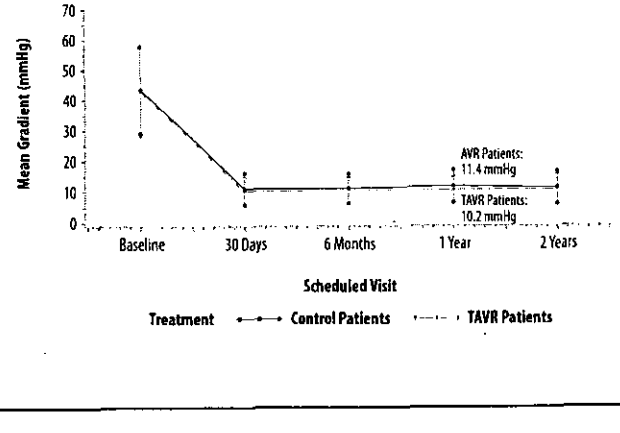
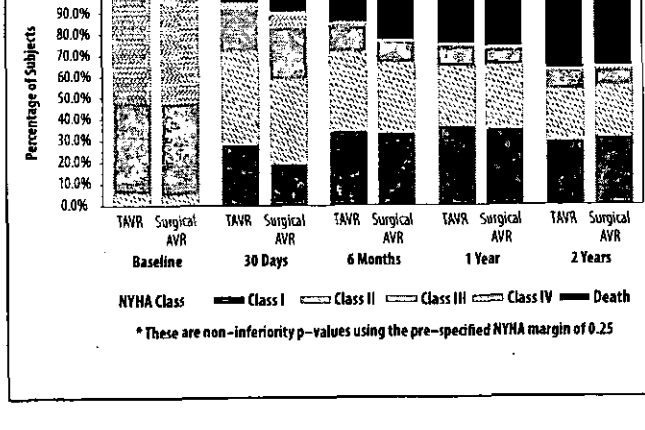


Figure 8. COHORT A - Secondary Endpoint:
NYHA at 2 Year Visit (AT Population)

THV274



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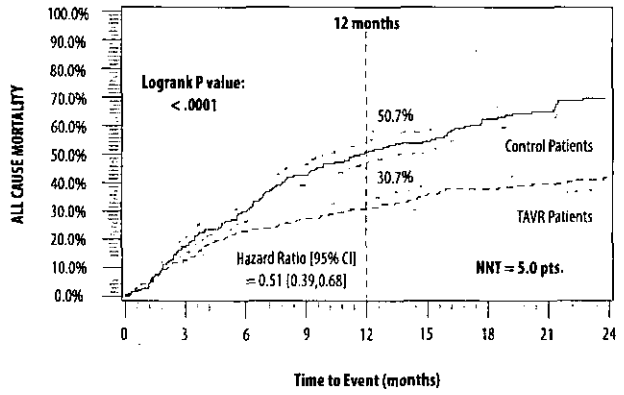
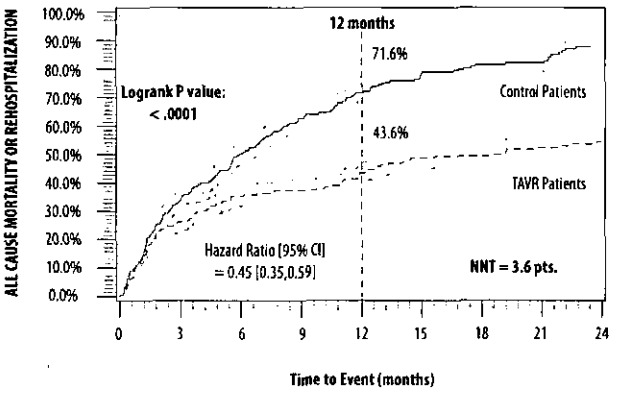
THV241

Figure 9. COHORT B - Primary Endpoint:
All Cause Mortality (ITT Population)
(68% confidence limits displayed)



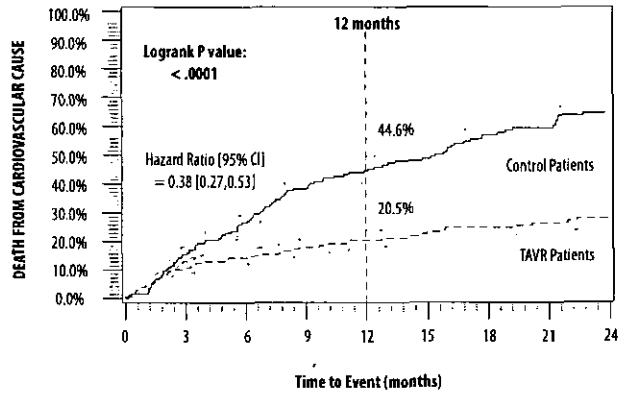
THV242

Figure 10. COHORT B - Co-Primary Endpoint:
Mortality or Repeat Hospitalization (ITT Population)
(68% confidence limits displayed)



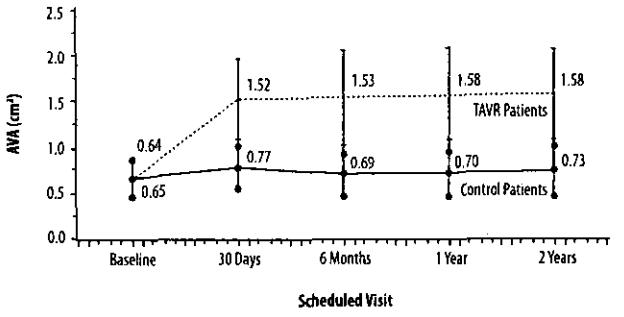
THV243

Figure 11. COHORT B - Secondary Endpoint:
Death from Cardiovascular Cause (ITT Population)
(68% confidence limits displayed)



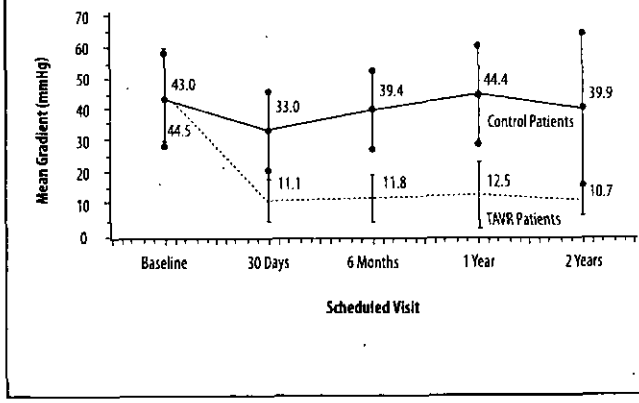
THV245

Figure 12. COHORT B - Secondary Endpoint:
AVA Over Time (ITT Population)
(one standard deviation displayed)



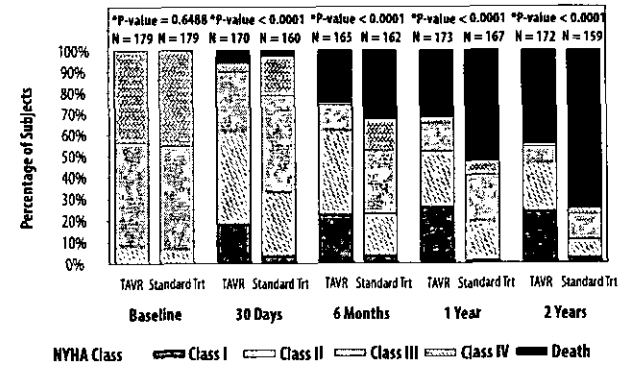
THV246

Figure 13. COHORT B - Secondary Endpoint:
Mean Gradient Over Time (ITT Population)
(one standard deviation displayed)



THV261

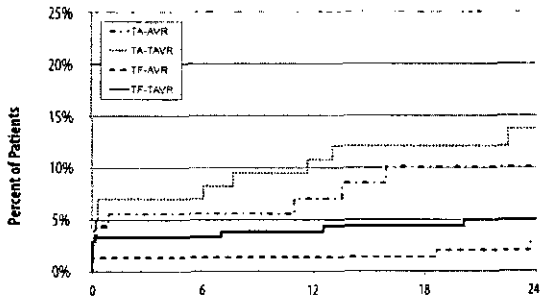
Figure 14. COHORT B - Secondary Endpoint:
NYHA at 2 Year Visit (ITT Population)



*These are superiority p-values computed using the method of Lachin

Figure 15. COHORT A - PMA Patients (AT)
Stroke Incidence

THV295



Patients at Risk		Months post Procedure			
TA-AVR	92	67	63	56	31
TA-TAVR	104	77	67	58	33
TF-AVR	221	170	160	150	108
TF-TAVR	240	204	182	165	113

Table 9: Stroke Incidence – COHORT A – PMA Patients (AT)

Months after procedure		0	6	12	18	24
TA-AVR	Patients at Risk	92	67	63	56	31
	Cumulative Incidence	1.1%	5.5%	7.0%	10.0%	10.0%
TA-TAVR	Patients at Risk	104	77	67	58	33
	Cumulative Incidence	0.0%	7.0%	10.8%	12.1%	13.8%
TF-AVR	Patients at Risk	221	170	160	150	108
	Cumulative Incidence	0.4%	1.4%	1.4%	1.4%	2.0%
TF-TAVR	Patients at Risk	240	204	182	165	113
	Cumulative Incidence	0.8%	3.4%	3.8%	4.4%	5.0%

Edwards

10/12

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Edwards Lifesciences

Edwards SAPIEN
Transcatheter Heart Valve with the Ascendra Balloon Catheter

Instructions for Use

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

Transapical Approach

Implantation of the transcatheter heart valve should be performed only by physicians who have received Edwards Lifesciences training. The implanting physician should be experienced in balloon aortic valvuloplasty.

Please verify that you have the latest version of the instructions for use prior to using the device by visiting http://THVIFU.edwards.com or by calling 1.800.822.9837. In order to access the instructions for use, an IFU Code will be required.

STERILE: The bioprosthesis is supplied sterilized with glutaraldehyde solution. The delivery system is supplied sterilized with ethylene oxide gas.

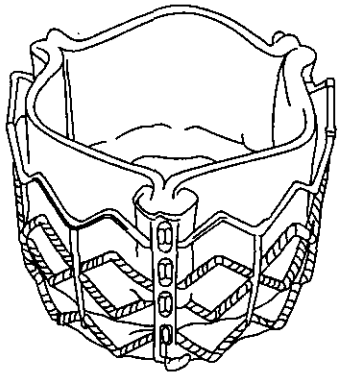
1.0 Device Description

- Edwards SAPIEN Transcatheter Heart Valve – Model 9000TFX (Figure 1)

The Edwards SAPIEN transcatheter heart valve (bioprosthesis) is comprised of a balloon-expandable, radiopaque, stainless steel (316 L) frame, three bovine pericardial tissue leaflets, and a polyethylene terephthalate (PET) fabric. The bioprosthesis is treated according to the Carpentier-Edwards ThermaFix process, packaged, and terminally sterilized in glutaraldehyde.

Figure 1. Edwards SAPIEN Transcatheter Heart Valve

THV01



Bioprosthesis Diameter	Frame Height (Profile)
23 mm	14.3 mm
26 mm	16.1 mm

The following table identifies the bioprosthesis size that should be used based on native valve annulus size, as measured by transesophageal echocardiography (TEE).

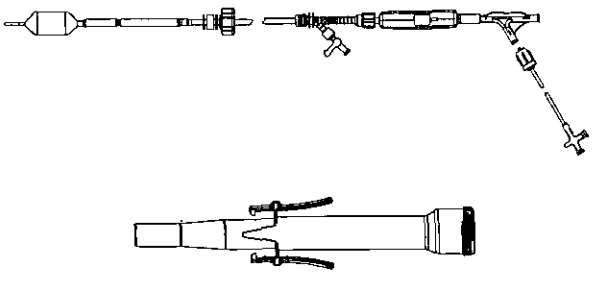
Native Valve Annulus Size (Tissue Annulus Diameter)	Bioprosthesis Diameter
18-22 mm	23 mm
21-25 mm	26 mm

- Ascendra Balloon Catheter – Model 9100BCL23 for 23 mm valve procedure and 9100BCL26 for 26 mm valve procedure (Figure 2)

  The Ascendra balloon catheter is used for transapical delivery of the Edwards SAPIEN transcatheter heart valve. The balloon catheter has radiopaque markers for visualization under fluoroscopy and a balloon for deployment of the bioprosthesis. The system also comes with a loader that is used to cover the bioprosthesis during delivery. An extension tubing is supplied for use with the balloon catheter during inflation.

Figure 2. Ascendra Balloon Catheter

THV207
THV108



2.0 Indications

The Edwards SAPIEN transcatheter heart valve, model 9000TFX, sizes 23 mm and 26 mm, is indicated for transapical delivery in patients with severe symptomatic calcified native aortic valve stenosis without severe aortic insufficiency and with ejection fraction > 20% who have been examined by a heart team including an experienced cardiac surgeon and a cardiologist

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and found to be operative candidates for aortic valve replacement but who have a Society of Thoracic Surgeons operative risk score ≥ 8% or are judged by the heart team to be at a ≥ 15% risk of mortality for surgical aortic valve replacement.

The Ascendra Balloon Catheter is indicated for the transapical delivery of the Edwards SAPIEN transcatheter heart valve.

3.0 Contraindications

The bioprosthesis and delivery system are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

4.0 Warnings

- Observation of the pacing lead throughout the procedure is essential to avoid the potential risk of pacing lead perforation.
- There is an increased risk of stroke in transcatheter aortic valve replacement procedures, as compared to balloon aortic valvuloplasty or other standard treatments.
- The devices are designed, intended, and distributed for single use only. **Do not re-sterilize or reuse the devices.** There are no data to support the sterility, non-pyrogenicity, and functionality of the devices after reprocessing.
- Incorrect sizing of the bioprosthesis may lead to paravalvular leak, migration, embolization and/or annular rupture.
- Accelerated deterioration of the bioprosthesis may occur in patients with an altered calcium metabolism. Bioprosthesis must remain hydrated at all times and cannot be exposed to solutions other than its shipping storage solution and sterile physiologic rinsing solution. Bioprosthesis leaflets mishandled or damaged during any part of the procedure will require replacement of the bioprosthesis.
- Caution should be exercised in implanting a bioprosthesis in patients with clinically significant coronary artery disease.
- Patients with pre-existing mitral valve devices should be carefully assessed prior to implantation of the bioprosthesis to ensure proper bioprosthesis positioning and deployment.
- Patients presenting with combination AV low flow, low gradient should undergo additional evaluation to establish the degree of aortic stenosis.
- Do not use the bioprosthesis if the tamper evident seal is broken, the storage solution does not completely cover the bioprosthesis, the temperature indicator has been activated, or the bioprosthesis is damaged, or the expiration date has elapsed.
- Do not mishandle the Ascendra Balloon Catheter or use it if the packaging or any components are not sterile, have been opened or are damaged (e.g. kinked or stretched), or the expiration date has elapsed.
- Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.
- Patient injury could occur if the delivery system is not un-flexed prior to removal.
- Care should be exercised in patients with hypersensitivities to chromium, nickel, molybdenum, manganese, copper, silicon, and/or polymeric materials.
- The procedure should be conducted under fluoroscopic guidance. Some fluoroscopically guided procedures are associated with a risk of radiation injury to the skin. These injuries may be painful, disfiguring, and long-lasting.
- The safety and efficacy of the transapical procedure has only been evaluated in those patient populations where the transfemoral procedure delivery is not suitable.

5.0 Precautions

- Long-term durability has not been established for the bioprosthesis. Regular medical follow-up is advised to evaluate bioprosthesis performance.
- Glutaraldehyde may cause irritation of the skin, eyes, nose and throat. Avoid prolonged or repeated exposure to, or breathing of, the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, refer to Material Safety Data Sheet available from Edwards Lifesciences.
- To maintain proper valve leaflet coaptation, do not overinflate the deployment balloon.
- Appropriate antibiotic prophylaxis is recommended post-procedure in patients at risk for prosthetic valve infection and endocarditis.
- Bioprosthetic valve recipients should be maintained on anticoagulant and antiplatelet therapy (e.g. clopidogrel or ticlopidine [75 mg/day]) for 6 months post procedure and aspirin (75-100 mg/day) for life, except when contraindicated, as determined by their physician.
- The safety of the bioprosthesis implantation has not been established in patients who have:
  - Pre-existing prosthetic heart valve or valve repair device in any position
  - Severe ventricular dysfunction with ejection fraction < 20%
  - Hypertrophic cardiomyopathy with or without obstruction (HOCM)
- Safety, effectiveness, and durability have not been established for valve-in-valve procedures.
- Safety and effectiveness have not been established for patients with the following characteristics/comorbidities:
  - Non-calcified aortic annulus
  - Congenital unicuspid or congenital bicuspid aortic valve
  - Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation > 3+)
  - Pre-existing prosthetic heart valve or prosthetic ring in any position
  - Severe mitral annular calcification (MAC), severe (> 3+) mitral insufficiency, or Gorlin syndrome
  - Blood dyscrasias defined as: leukopenia (WBC < 3000 mm^3), acute anemia (Hb < 9 mg%), thrombocytopenia (platelet count < 50,000 cells/mm^3), or history of bleeding diathesis or coagulopathy
  - Hypertrophic cardiomyopathy with or without obstruction (HOCM)

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- Echocardiographic evidence of intracardiac mass, thrombus, or vegetation
- A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media, which cannot be adequately premedicated
- Native aortic annulus size < 18 mm or > 25 mm as measured by echocardiogram
- Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5 cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding, or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe "unfolding" and tortuosity of the thoracic aorta
- Bulky calcified aortic valve leaflets in close proximity to coronary ostia

6.0 Potential Adverse Events

Potential risks associated with the overall procedure including potential access complications associated with standard cardiac catheterization for the transapical access procedure, balloon valvuloplasty, the potential risks of conscious sedation and/or general anesthesia, and the use of angiography:

- Death
- Stroke/transient ischemic attack clusters or neurological deficit
- Paralysis
- Permanent disability
- Respiratory insufficiency or respiratory failure
- Hemorrhage requiring transfusion or intervention
- Infundibulum injury
- Cardiovascular injury including perforation or dissection of vessels, ventricle, myocardium or valvular structures that may require intervention
- Annular tear or rupture
- Pericardial effusion or cardiac tamponade
- Embolization including air, calcific valve material or thrombus
- Thrombus formation, plaque dislodgment, and embolization that may result in myocardial infarction, stroke, distal peripheral occlusion, and/or death
- Infection including septicemia and endocarditis
- Heart failure
- Myocardial infarction
- Valve leaflet dehiscence
- Renal insufficiency or renal failure
- Conduction system injury (defect) which may require a permanent pacemaker
- Arrhythmia
- Retroperitoneal bleed
- Femoral AV fistula or pseudoaneurysm
- Reoperation
- Peripheral ischemia or nerve injury
- Restenosis
- Pulmonary edema
- Pleural effusion
- Bleeding
- Balloon rupture
- Balloon separation following balloon rupture
- Anemia
- Abnormal lab values (including electrolyte imbalance)
- Hypertension or hypotension
- Allergic reaction to anesthesia or to contrast media
- Hematoma
- Syncope
- Pain or changes at the access site
- Exercise intolerance or weakness
- Inflammation
- Angina
- Heart murmur
- Fever
- Mechanical failure of delivery system and/or accessories
- Suturing of a peripheral coronary artery
- Valvular tearing or trauma

Additional potential risks specifically associated with the use of the bioprosthesis include, but may not be limited to the following:

- Cardiac arrest
- Cardiogenic shock
- Emergency cardiac surgery
- Cardiac failure or low cardiac output
- Coronary flow obstruction/transvalvular flow disturbance
- Injury at the site of ventricular access that may require repair
- Device thrombosis requiring intervention
- Valve thrombosis
- Device embolization
- Device migration or malposition requiring intervention
- Valve deployment in unintended location

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- Valve stenosis
- Structural valve deterioration (wear, fracture, calcification, leaflet tear/ tearing from the stent posts, leaflet retraction, stent creep, suture line disruption of components of a prosthetic valve, thickening, stenosis)
- Device degeneration
- Paravalvular or transvalvular leak
- Injury to the mitral valve
- Valve regurgitation
- Hemolysis
- Device explants
- Nonstructural dysfunction
- Non-emergent reoperation

All listed risks may include symptoms associated with the above mentioned medical conditions.

7.0 Directions for Use

7.1 Required Equipment

- Edwards SAPIEN Transcatheter Heart Valve
- Accessories required for the transcatheter aortic valve replacement procedure:
  - Ascendra Balloon Catheter
  - 20 mm balloon valvuloplasty catheter such as Ascendra Balloon Aortic Valvuloplasty Catheter Model 9100BAVC
  - Ascendra Introducer Sheath Set Model 9100IS
  - Crimper Model 9100CR23 for 23 mm valve procedure and Model 9100CR26 for 26 mm valve procedure
  - Inflation device provided by Edwards Lifesciences for this application
- Standard cardiac catheterization lab equipment
- Fluoroscopy (fixed, mobile or semi-mobile fluoroscopy systems appropriate for use in percutaneous coronary interventions)
- Transesophageal or transthoracic echocardiography capabilities
- Exchange length 0.035 inch (0.89 mm) soft, standard and extra-stiff guidewires
- Temporary pacemaker (PM) and pacing lead
- Sterile rinsing basins, physiological saline, heparinized saline, and 15% diluted radiopaque contrast medium
- 20 cc or larger luer-lock syringe
- 60 cc or larger luer-lock syringe
- High-pressure 3-way stopcock

7.2 Bioprosthesis Handling and Preparation

Follow sterile technique during device preparation and implantation.

7.2.1 Bioprosthesis Rinsing Procedure

The bioprosthesis is packaged sterile in a plastic jar with a screw-cap closure and seal. Before opening, carefully examine the jar for evidence of damage (e.g. a cracked jar or lid, leakage, or broken or missing seals).

CAUTION: Bioprostheses from containers found to be damaged, leaking, without adequate sterilant, or missing intact seals must not be used for implantation.

Step	Procedure
1	Set up two (2) sterile bowls with at least 500 mL of sterile physiological saline to thoroughly rinse the glutaraldehyde sterilant from the bioprosthesis.
2	The bioprosthesis is contained in the jar within a holder. Carefully remove the bioprosthesis/holder assembly from the jar without touching the tissue. The holder is tagged with the bioprosthesis' serial identification number. Inspect the bioprosthesis for any signs of damage to the frame or tissue.
3	Rinse the bioprosthesis as follows: Place the bioprosthesis in the first bowl of sterile physiological saline. Be sure the saline solution completely covers the bioprosthesis and holder. With the bioprosthesis and holder submerged, slowly agitate (to **gently** swirl the bioprosthesis and holder) back and forth for a minimum of 1 minute. Transfer the bioprosthesis and holder to the second rinsing bowl of physiological saline and gently agitate for at least 1 more minute. Ensure the rinse solution in the first bowl is not used. The bioprosthesis should be left in the final rinse solution until needed to prevent the tissue from drying. **CAUTION: Do not allow the bioprosthesis to come in contact with the bottom or sides of the rinse bowl during agitation or swirling of the bioprosthesis. Care must be taken to ensure that the identification tag does not come in contact with the tissue and damage it. No other objects should be placed in the rinse bowls. The bioprosthesis should be kept hydrated throughout the rest of the preparation procedure to prevent the tissue from drying.**

7.2.2 Prepare Transapical Procedure Components

Step	Procedure
1	Refer to Ascendra Introducer Sheath Set and Crimper instructions for use on device preparation and handling.
2	Remove the balloon cover from the Ascendra Balloon Catheter.
3	Loosen the pusher nut and slide the pusher as far proximal as possible. Rotate the pusher nut to secure the pusher. Slide the loader cap, washers, and seal as far proximal as possible. **CAUTION: Overtightening the pusher nut may result in improper balloon inflation.**
4	Prime and flush the guidewire lumen of the balloon catheter with heparinized saline.

Step	Procedure
5	Insert an extra-stiff guidewire (0.035" [0.89 mm] and ≥ 100 cm long) in the guidewire lumen, leaving a 2 to 3 cm segment of the guidewire protruding from the distal tip.
6	Flush the balloon catheter with heparinized saline through the flush port.
7	Attach extension tubing to balloon inflation port.
8	Prepare a 60 mL or larger luer-lock syringe with diluted contrast medium (15:85 contrast to heparinized saline) and attach it to the balloon extension tubing.
9	Completely fill the inflation device provided by Edwards Lifesciences with diluted contrast medium and attach to the balloon extension tubing.
10	Close stopcock to inflation device. De-air the balloon catheter.
11	Close the stopcock to the syringe. Insert the balloon into the balloon gauge located on the Crimper. Inflate the balloon and verify its diameter fits the gauge with minimal friction. While gently pulling and pushing the balloon, verify that the balloon moves with some resistance within the balloon gauge. If the balloon does not reach the correct diameter when fully inflated, add or discard some of the inflation solution in the inflation device provided by Edwards Lifesciences until the correct diameter is reached. The inflation device must remain connected to the balloon catheter throughout the rest of the procedure. **Note:** Correct balloon sizing is critical to successful valve deployment and valve function.
12	Close stopcock to the balloon catheter and remove any remaining diluted contrast medium in the inflation device to the syringe. Lock the inflation device provided by Edwards Lifesciences.
13	Close the stopcock to the syringe and verify the balloon is sized appropriately with the balloon gauge. Remove the syringe.
14	Unlock inflation device provided by Edwards Lifesciences and deflate the balloon while creating a three-wing fold configuration, and ensure no diluted contrast medium is left behind. Lock the inflation device provided by Edwards Lifesciences.

7.2.3 Mount and Crimp the Bioprosthesis on the Balloon Catheter

Step	Procedure
1	Remove the bioprosthesis from the holder and gently place the bioprosthesis into the crimper aperture.
2	Gradually crimp the bioprosthesis to a diameter of approximately 12 mm.
3	Remove the bioprosthesis from the crimper and place it on the balloon catheter with the inflow (fabric cuff end) of the bioprosthesis towards the **proximal end** of the balloon catheter. Center bioprosthesis between the radiopaque markers.
4	Place the bioprosthesis back in the crimper aperture, and completely crimp until it fits inside the crimp gauge. **CAUTION: The physician must verify correct mounting/ orientation of the bioprosthesis prior to its implantation.**
5	Loosen the pusher nut and advance the pusher to align the pusher tip with the proximal end of the crimped bioprosthesis. Rotate the pusher nut to secure the pusher in place. **CAUTION: Overtightening the pusher nut may result in improper balloon inflation.**
6	Flush the loader with sterile heparinized saline and slide the threaded end of the loader over the crimped bioprosthesis.
7	Slide the washers and seal on the balloon catheter shaft distally to the pusher. Insert into loader. Ensure washers and seal are flat against each other within the loader to prevent leakage. Slide loader cap distally over balloon catheter so it sits flat against the washers and seal and rotate the loader cap onto the base of loader. Check that the thread is not exposed. This indicates that the loader cap and seal are fully engaged around the pusher tubing. Do not overtighten the loader cap. **Note: The loader must fully cover the bioprosthesis.**
8	Re-flush the balloon catheter through the flush port and close stopcock to the balloon catheter. **Note: Keep bioprosthesis hydrated until ready for implantation.**
9	Remove guidewire and flush guidewire lumen.

7.3 Valvuloplasty and Bioprosthesis Delivery

Valvuloplasty and bioprosthesis delivery should be performed under general anesthesia with hemodynamic monitoring in a catheterization lab/hybrid operating room with fluoroscopic and echocardiographic imaging capabilities.

Administer heparin to maintain the ACT at ≥ 250 sec.

CAUTION: Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.

7.3.1 Baseline Parameters

Step	Procedure
1	Perform a supra-aortic angiogram with the projection of the native aortic valve perpendicular to the view.
2	Evaluate the height between the inferior aspect of the annulus and the inferior aspects of the lowest coronary ostium for subsequent prosthetic aortic valve implantation.
3	Introduce a pacemaker (PM) lead until its distal end is positioned in the right ventricle.
4	Set the stimulation parameters, and test pacing.

7.3.2 Valvuloplasty

Refer to Ascendra Balloon Aortic Valvuloplasty Catheter Instructions for Use (IFU) for information on device preparation and handling.

Note: Rapid ventricular pacing should be performed when using the Ascendra Balloon Aortic Valvuloplasty Catheter for valvuloplasty prior to transcatheter valve implantation.

After placement of the balloon at the intended site, begin rapid ventricular pacing. Once the blood pressure has decreased to 50 mmHg or below, balloon inflation can commence.

CAUTION: Prosthetic valve implantation should not be carried out if the balloon cannot be fully inflated during valvuloplasty.

7.3.3 Bioprosthesis Delivery

Step	Procedure
1	Insert the introducer sheath. Refer to the Ascendra Introducer Sheath Set IFU for additional information on device preparation and handling.
2	Advance balloon catheter over guidewire. Insert loader into the sheath until it locks. Tap lightly on the loader and loosen the loader cap to de-air. Tighten cap until loader is sealed and catheter can move with minimal resistance. Check that the thread is not exposed. This indicates that the loader cap and seal are fully engaged around the pusher tubing. Do not overtighten.
3	Cross the native aortic valve and position the bioprosthesis within the diseased valve.
4	Loosen the pusher nut and retract the pusher, leaving the bioprosthesis in position. Rotate the pusher nut to secure the pusher. Verify that the pusher is completely off of the balloon before it is inflated and the bioprosthesis is deployed. **CAUTION: The pusher must be pulled back for proper balloon inflation and bioprosthesis deployment.**
5	Position the mid-point of the bioprosthesis at the plane of the hinge points of the native valve leaflets.
6	Verify the correct location of the bioprosthesis with respect to the calcified valve.
7	Begin bioprosthesis deployment: • Unlock the inflation device. • Begin rapid pacing; once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. • Deploy the bioprosthesis by inflating the balloon with the entire volume in the inflation device. When the balloon catheter has been completely deflated, turn off the pacemaker. • If deflection was used, straighten the catheter tip. • Retract the balloon catheter into the introducer sheath.
8	Disengage loader from sheath and remove balloon catheter.
9	Remove sheath when the ACT level is appropriate (e.g. reaches < 150 sec). Close apical access site.

8.0 How Supplied

STERILE: The bioprosthesis is supplied sterilized with glutaraldehyde solution. The balloon catheter is supplied sterilized with ethylene oxide gas.

8.1 Storage

The bioprosthesis must be stored between 10 °C-25 °C (50 °F-77 °F). Each jar is shipped in an enclosure containing a temperature indicator to detect exposure of the bioprosthesis to extreme temperature.

The Ascendra Balloon Catheter should be stored in a cool, dry place.

9.0 MR Safety

MR Conditional

Non-clinical testing has demonstrated that the Edwards SAPIEN THV (implant) is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 Tesla (T) or 3 Tesla.
- Spatial gradient field of 2500 Gauss/cm or less.
- Maximum whole-body-averaged specific absorption rate (SAR) of 2 W/kg for 15 minutes of scanning.
- Normal mode operation, as defined in IEC 60601-2-33 Ed. 3.0, of the MR system.

In non-clinical testing and analysis, the implant was determined to produce a temperature rise of less than 1.1 °C above background for a whole body SAR of 2.0 W/kg for 15 minutes of MR scanning in a 1.5 T Cylindrical whole body MR system, assessed using a GE Signa whole body coil and a phantom designed to simulate human tissue. The phantom average SAR calculated using calorimetry was 2.2 W/kg and local background SAR at the site of the implant was 5.6 W/kg. The measured rise above background was 0.7 °C for a whole body SAR of 2 W/kg in a 3.0 T cylindrical bore whole body MR system, assessed using a GE Signa HDx whole body active shield MR scanner with software version 14/LX/MR and a phantom designed to simulate human tissue. The phantom average SAR calculated using calorimetry was 2.9 W/kg and local background SAR at the site of the implant was 8.4 W/kg.

The image artifact extended as far as 15 mm from the implant for spin echo images and 40 mm for gradient images when scanned in non-clinical testing in a 3.0 T GE Signa HDx MR system. The implant has not been evaluated in MR systems other than 1.5 or 3.0 T.

10.0 Patient Information

Patient education brochures are provided to each site and should be given to the patient to inform them of the risks and benefits of the procedure and alternatives in adequate time before the procedure to be read and discussed with their physician. A copy of this brochure may also be obtained from Edwards Lifesciences by calling 1.800.822.9837. A patient registration form is provided with each transcatheter heart valve. After implantation, all requested information should be completed on this form. The serial number may be found on the package and on the identification tag attached to the transcatheter heart valve. The original form should be returned to the Edwards Lifesciences address indicated on the form and upon receipt, Edwards Lifesciences will provide an identification card to the patient.

11.0 Recovered Clinical Bioprosthesis

The explanted bioprosthesis should be placed into a suitable histological fixative such as 10% formalin or 2% glutaraldehyde and returned to the

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company. Refrigeration is not necessary under these circumstances. Contact Edwards Lifesciences to request an Explant Kit.

Disposal of Used Devices

Used devices may be disposed of in the same manner that hospital waste and biohazardous materials are handled. There are no special risks related to the disposal of these devices.

12.0 Clinical Studies

The placement of aortic transcatheter valves (PARTNER) trial, a prospective, randomized-controlled, multi-center pivotal trial, evaluated the safety and effectiveness of the Edwards SAPIEN transcatheter heart valve via transfemoral and transapical delivery in a stratified population of high-risk and inoperable patients with severe symptomatic native aortic stenosis. Patients were stratified into two cohorts based on their risk of operability for standard aortic valve replacement surgery – those who were considered high surgical risk were eligible for Cohort A, while inoperable patients were eligible for Cohort B due to coexisting conditions that resulted in the probability of death or irreversible morbidity exceeding 50%.

Study Design – Cohort A

This was a randomized study with the primary objective of ascertaining if TAVR is non-inferior to AVR surgery (7.5% margin) with respect to 12-month survival outcomes in high-risk surgical patients. Other objectives were focused on characterizing the benefit to risk ratio of TAVR relative to AVR.

Patients in Cohort A were first evaluated for vascular access to determine whether their peripheral arteries could accommodate the 22 or 24 French sheaths required for the transfemoral TAVR approach to deliver the 23 mm or 26 mm Edwards SAPIEN valve sizes. Those patients who could accommodate these sheaths were then randomized 1:1 between transfemoral TAVR and surgical AVR. Those patients whose arteries could not accommodate these sheaths were randomized 1:1 between transapical TAVR and surgical AVR.

The primary study endpoint was based on a pooled transapical and transfemoral analysis, and was defined as freedom from all cause mortality at one year for the high-risk cohort. All patients were followed for at least 1 year, and cross-over from the surgical AVR group to the TAVR group was not permitted, except when findings or events during the assigned procedure prevented the planned treatment. Clinically important endpoints included neurological adverse events, aortic regurgitation, bleeding, and vascular complications. In addition, the Sponsor prespecified secondary endpoints included the following: time from randomization to the first occurrence of a Major Adverse Cardiac and Cerebrovascular Event (MACCE) within one year for which MACCE definition was comprised of death, MI, stroke, and renal failure as defined by protocol, total hospital days through one year, NYHA functional class at one year, and 6-minute walk test at one year. Additional prespecified efficacy endpoints were measured at 30 days, six months, and one year for the following: functional improvement from baseline as measured per (1) NYHA functional classification, (2) EOA, and (3) 6-minute walk test, freedom from MACCE, improved Quality of Life (QoL), and improved valve function demonstrated by an improvement in EOA.

Study Design – Cohort B

This was a randomized study with the primary objective of ascertaining if TAVR is superior to standard therapy (including balloon aortic valvuloplasty) in a control group for inoperable patients with respect to 12-month survival outcomes. Other objectives were focused on characterizing the benefit to risk ratio of TAVR relative to the standard therapy control group.

Patients in Cohort B were also evaluated for vascular access and those meeting the criteria were randomized 1:1 to either transfemoral delivery of the Edwards SAPIEN valve or to a control group. Patients in the control group were treated with medication and/or balloon valvuloplasty. Patients in Cohort B who did not meet the criteria for vascular access were not eligible for the trial. The transapical procedure was not utilized in the study of these inoperable patients.

Study Results – Cohort A

A total of 699 (657 in the As-Treated [AT] population) high-risk patients with severe aortic stenosis were enrolled at 26 centers (23 in the United States) and assigned to TAVR (344 patients) or AVR (313 patients) with baseline characteristics described in Table 1. Among the TAVR patients, 240 were treated using transfemoral access and 104 were treated using transapical access. Severe aortic stenosis was defined as a mean gradient > 40 mmHg, jet velocity > 4.0 m per sec, or an initial aortic valve area (AVA) of 0.8 cm^2. The primary endpoint for the high-risk cohort was freedom from all cause mortality at one year. Clinical outcomes of TAVR (transfemoral and transapical) as compared to AVR are summarized in Tables 5, 6, and 7. There was a failure of attempt to treat 11% of the patients in the AVR arm and the inclusion of additional surgical procedures (such as coronary bypass grafting and operation to correct other valve lesions) in 13% of the AVR patients. The immediate conversion to surgical AVR in patients with failed TAVR occured in 2.3% of the TAVR patients. The time from randomization to treatment in the TAVR arm was 10.6 days versus 15.6 days in the AVR arm ($P < 0.001$). At day 365, the Kaplan-Meier estimate of all cause death was 23.7% in the TAVR group, as compared to 25.2% in the AVR group. The estimated difference between these treatment groups is -1.5% with a one-sided lower 95% confidence interval for the difference of -4.0%, which is smaller than the pre-specified margin of -7.5%. The non-inferiority p-value for this difference is 0.0037, indicating that TAVR is non-inferior to AVR with respect to all cause death [Figure 3]. Pre-specified secondary endpoints included valve performance [Figures 6 and 7] and NYHA functional class [Figure 8]. When interpreting NYHA results, consider that the evaluation was unblinded. As with other heart valve trials, the patients are aware of their treatment group. Accordingly there is the potential for bias in the NYHA values, and there is no statistical method for estimating the bias. At 30 days, TAVR was more likely than AVR to reduce cardiac symptoms (New York Heart Association class ≤ II) ($P < 0.0030$). At 1 year, both TAVR and AVR improved cardiac symptoms with no evidence of treatment differences. The majority of strokes were reported at ≤ 30 days; the rate was 4.4% in the TAVR arm and 2.6% in the AVR arm ($P = 0.2064$). At one year, the rate of stroke was 5.8% in the TAVR arm and 3.0% in the AVR arm ($P = 0.0887$). At one year, the rate of mild aortic insufficiency was 50% in the TAVR arm and 18% in the AVR arm, the rate of moderate or greater aortic insufficiency was 23% in the TAVR arm and 3% in the AVR arm. Hemorrhagic/vascular events occurred in 24.5% of TAVR patients as compared to 27.8% of AVR patients between 0 and 30 days ($P = 0.3332$). Between 0 days and one year, hemorrhagic/vascular events occurred in 26.8% of TAVR patients as compared to 28.6% of AVR patients ($P = 0.6248$). Bleeding events occurred in 10.2% of TAVR patients vs. 28.4% of AVR patients ($P < 0.0001$) between 0 and 30 days and in 10.2% of TAVR patients vs. 28.4% of AVR patients between 0 and 365 days ($P < 0.0001$). Aortic valve gradients and areas improved significantly after TAVR and AVR at 30 days and 1 year. There were small differences in aortic valve gradients and areas favoring TAVR (at 1 year, mean gradient 10.2 vs. 11.4 mmHg; $P = 0.0131$ and valve area 1.59 vs. 1.44 cm^2; $P = 0.0027$). Mild para-valvular regurgitation was more frequent after TAVR than AVR (at 30 days, 49% vs 7%, respectively with a $P < 0.0001$, at 1 year, 50% vs 9% $P < 0.0001$) and moderate or severe para-valvular regurgitation, was also more frequent after TAVR than AVR (at 30-days, 11.7% vs. 0.9%, respectively, with $P < 0.0001$; at 1-year, 6.5% vs. 1.9%,

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respectively, with $P < 0.0469$). Mild and greater para-valvular regurgitation was found to be associated with late mortality. There were important differences in mortality outcomes for males and females comparing TAVR versus AVR therapies where males had similar 1 and 2 year mortality to AVR (28.5% and 25.2% at 1 year and 37.9% and 32.6% at 2 years respectively) and females had less frequent mortality with TAVR than AVR (18.5% and 29% at one year and 28.5% and 38.1% at 2 years respectively). Notably, baseline characteristics were different among males and females despite similar STS scores, where women were slightly older and were more frequently frail but males had a higher frequency of many important co-morbidities compared to the women, especially cardiovascular disease. This could explain the difference in 1 and 2 year mortality.

In patients with severe aortic stenosis who are at high-risk for operation, TAVR and AVR had similar survival after 1 year and similar improvement in cardiac symptoms. TAVR patients experienced a two times higher incidence of strokes and three times higher incidence of major vascular events. AVR patients experienced a two times higher incidence of bleeding. With respect to the transfemoral approach in both the ITT and AT populations, all cause mortality in the TAVR arm (22.2% and 21.4% respectively) was non-inferior to all cause mortality in the AVR arm (26.4% and 25.2% respectively) at 1 year. With respect to the transapical approach in both the ITT and AT populations, all cause mortality was higher in the TAVR arm (29.0% and 29.1% and 27.9% and 25.3% in the AVR arm respectively) at 1 year. The study was not powered for this analysis. In conclusion, when used in the high surgical risk population mortality associated with TAVR is not inferior to the mortality associated with surgical AVR at one year, but has double the stroke rate, three times the vascular complication rate, but half the bleeding rate.

Study Results – Cohort B

A total of 358 patients (ITT population) with severe aortic stenosis were enrolled and underwent 1:1 randomization at 22 centers (18 in the United States) with baseline characteristics described in Table 2. Severe aortic stenosis was defined as an aortic-valve area of less than 0.8 cm^2, a mean aortic-valve gradient of 40 mmHg or more, or a peak aortic-jet velocity of 4.0 m per second or more. The primary end point was the rate of death from any cause over the duration of the trial. At 1 year, the rate of death from any cause (Kaplan-Meier analysis) was 30.7% with TAVR, as compared with 50.7% in the group not receiving the valve (hazard ratio with TAVR, 0.51; 95% confidence interval [CI], 0.39 to 0.68; $P < 0.0001$) (Figure 9). A total of 141 of the 179 (78.8%) patients in the control group underwent balloon aortic valvuloplasty (BAV). In addition, 11 patients (6.1%) underwent aortic valve replacement. 5 patients (2.8%) received an LV-descending aortic conduit, and 4 patients (2.2%) received a THV outside the US. The co-primary composite end point was time of death from any cause or the time to the first occurrence of repeat hospitalization. The rate of the composite end point of death from any cause or repeat hospitalization was 43.6% with TAVR as compared with 71.6% in the control group (hazard ratio, 0.45; 95% CI, 0.35 to 0.59; $P < 0.0001$) (Figure 10). Prespecified secondary end points included the rate of death from cardiovascular causes (Figure 11), NYHA functional class (Figure 14), valve performance (Figures 12 and 13), and the distance covered during a 6-minute walk test. Among survivors at 1 year, the rate of cardiac symptoms (New York Heart Association class III or IV) was lower among patients who had undergone TAVR than among those in the control group (23.9% vs. 60.8%, $P < 0.001$). When interpreting NYHA results, consider that the evaluation was unblinded. As with other heart valve trials, the patients are aware of their treatment group. Accordingly there is the potential for bias in the NYHA values, and there is no statistical method for estimating the bias. At 30 days, TAVR, as compared with the control, was associated with a higher incidence of strokes (7.3% vs. 1.7%, $P = 0.02$) and major vascular complications (16.8% vs. 1.1%, $P < 0.0001$). The time from index procedure to stroke in the TAVR group was as follows: 1 stroke at 12 days before the index procedure but after randomization, 4 strokes on the day of the index procedure, 2 strokes on the first post-operative day and 2 on the second post-operative day, and one stroke each on days 3, 5, 10, 23, 39, 51, 75, 120, 136, and 151. At 1 year, the rate of hemorrhagic vascular complication was 34.3% in the TAVR group, as compared to 17.7% in the control group. At 1 year, the rate of bleeding events was 17.3% in the TAVR group, as compared to 2.2% in the control group. Additionally, at 1 year, the rate of endocarditis was 1.4% in the TAVR group, as compared to 0.8% in the control group. Mean index hospital stay was 8.5 days for the TAVR group, as compared to 7.6 days for the control group. Mean days alive out of hospital was 273.8 days for the TAVR group and 210.2 days for the control group. At 1 year, the rate of aortic regurgitation for the TAVR group was as follows: 2% of patients at 4+, 13% of patients at 3+, 50% of patients at 2+, 20% of patients at 1+, and 11% of patients with no regurgitation. In comparison, the rate of aortic regurgitation of the control group was as follows: 17% of patients at 3+, 39% of patients at 2+, 37% of patients at 1+, and 7% of patients with no regurgitation.

Procedure data for the TAVR group is summarized in Table 4. Clinical outcomes of TAVR as compared with the control are summarized in Table 8. In the two years after TAVR, there was no deterioration in the functioning of the bioprosthetic valve, as assessed by evidence of stenosis or regurgitation on an echocardiogram.

Additional data for the inoperable patient population in Cohort B has been collected, reviewed, and adjudicated; results are summarized in Table 8.

In patients with severe aortic stenosis who were not suitable candidates for surgery, TAVR, as compared with the control, significantly reduced the rates of death from any cause, the composite end point of death from any cause or repeat hospitalization, and cardiac symptoms, despite the higher incidence of stroke and major vascular events.

These products are manufactured and sold under one or more of the following US patent(s): US Patent No. 5,411,552; 5,931,969; 6,210,957; 6,214,054; 6,547,827; 6,561,970; 6,899,704; 6,908,481; 7,214,344; 7,510,575; 7,530,253; and RE40570 and corresponding foreign patents. Additional patents are pending.

Table 1: COHORT A – Baseline Characteristics of the Patients and Echocardiographic Findings* (AT Population)							
	Transapical Approach		Transfemoral Approach		Pooled Approaches		P Value
Characteristic	AVR (N = 92)	TAVR (N = 104)	AVR (N = 221)	TAVR (N = 240)	AVR (N = 313)	TAVR (N = 344)	
Age – yr	83.4 ± 5.5	82.9 ± 7.0	84.8 ± 6.6	83.9 ± 6.8	84.4 ± 6.3	83.6 ± 6.8	0.12
Male sex – no. (%)	55 (59.8)	53 (51.0)	124 (56.1)	145 (60.4)	179 (57.2)	198 (57.6)	0.94
STS score†	12.01 ± 3.5	11.7 ± 3.6	11.5 ± 3.3	11.9 ± 3.2	11.7 ± 3.4	11.8 ± 3.3	0.65
NYHA class – no. (%):							
II	4/92 (4.3)	8/104 (7.7)	12/221 (5.4)	12/240 (5.0)	16/313 (5.1)	20/344 (5.8)	0.73
III or IV	88/92 (95.7)	96/104 (92.3)	209/221 (94.6)	228/240 (95.0)	297/313 (94.9)	324/344 (94.2)	> 0.999
Coronary artery disease – no. (%)	76/92 (82.6)	77/104 (74.0)	165/221 (74.7)	181/240 (75.4)	241/313 (77.0)	258/344 (75.0)	0.58
Previous myocardial infarction – no./total no. (%)	34/92 (37.0)	28/104 (26.9)	56/218 (25.7)	64/239 (26.8)	90/310 (29.0)	92/343 (26.8)	0.54
Previous intervention – no./total no. (%):							
CABG	51/92 (55.4)	51/104 (49.0)	88/221 (39.8)	95/240 (39.6)	139/313 (44.4)	146/344 (42.4)	0.64
PCI	39/91 (42.9)	33/104 (31.7)	62/221 (28.1)	82/238 (34.5)	101/312 (32.4)	115/342 (33.6)	0.74
Balloon aortic valvuloplasty	10/92 (10.9)	13/104 (12.5)	22/221 (10.0)	33/240 (13.8)	32/313 (10.2)	46/344 (13.4)	0.2287
Cerebral vascular disease – no./total no. (%)	26/86 (30.2)	40/96 (41.7)	53/206 (25.7)	56/227 (24.7)	79/292 (27.1)	96/323 (29.7)	0.48
Peripheral vascular disease – no./total no. (%)	56/90 (62.2)	65/103 (63.1)	76/217 (35.0)	83/238 (34.9)	132/307 (43.0)	148/341 (43.4)	0.94
COPD – no./total no. (%):							
Any	41/92 (44.6)	46/104 (44.2)	97/221 (43.9)	104/240 (43.3)	138/313 (44.1)	150/344 (43.6)	0.94
Oxygen-dependent	7/92 (7.6)	11/104 (10.6)	16/221 (7.2)	21/240 (8.8)	23/313 (7.3)	32/344 (9.3)	0.90
Creatinine > 2 mg/dl (177 µmol/liter) – no./total no. (%)	9/92 (9.8)	7/103 (6.8)	11/221 (5.0)	30/237 (12.7)	20/313 (6.4)	37/340 (10.9)	0.05
Atrial fibrillation – no./total no. (%)	17/33 (51.5)	31/58 (53.4)	51/121 (42.1)	49/138 (35.5)	68/154 (44.2)	80/196 (40.8)	0.59
Permanent pacemaker – no./total no. (%)	17/92 (18.5)	21/104 (20.2)	53/221 (24.0)	48/240 (20.0)	70/313 (22.4)	69/344 (20.1)	0.50
Pulmonary hypertension – no./total no. (%)	38/92 (41.3)	55/104 (52.9)	112/221 (50.7)	117/240 (48.8)	150/313 (47.9)	172/344 (50.0)	0.07
Extensively calcified aorta – no. (%)	1/92 (1.1)	2/104 (1.9)	1/221 (0.5)	0/240 (0.0)	2/313 (0.6)	2/344 (0.6)	> 0.999
Deleterious effects of chest-wall irradiation – no. (%)	0/92 (0.0)	2/104 (1.9)	2/221 (0.9)	1/240 (0.4)	2/313 (0.6)	3/344 (0.9)	> 0.999
Chest-wall deformity – no. (%)	1/92 (1.1)	0/104 (0.0)	0/221 (0.0)	0/240 (0.0)	1/313 (0.3)	0/344 (0.0)	0.48
Liver disease – no./total no. (%)	0/92 (0.0)	2/104 (1.9)	9/221 (4.1)	6/240 (2.5)	9/313 (2.9)	8/344 (2.3)	0.81
Echocardiographic findings:							
Aortic-valve area – cm^2 (n, mean)	88, 0.7 ± 0.2	95, 0.7 ± 0.2	207, 0.6 ± 0.2	223, 0.7 ± 0.2	295, 0.6 ± 0.2	318, 0.7 ± 0.2	0.28
Mean aortic-valve gradient – mmHg (n, mean)	90, 40.5 ± 12.9	97, 41.7 ± 13.9	210, 44.6 ± 14.8	229, 43.0 ± 14.8	300, 43.4 ± 14.3	326, 42.6 ± 14.5	0.49
Mean LVEF – (n, mean)	89, 53.5 ± 10.9	98, 53.6 ± 12.2	211, 53.3 ± 13.3	232, 52.2 ± 14.0	300, 53.3 ± 12.6	330, 52.6 ± 13.5	0.48
Moderate or severe mitral regurgitation – no./total no. (%)¶	19/89 (21.3)	19/99 (19.2)	44/208 (21.2)	46/230 (20.0)	63/297 (21.2)	65/329 (19.8)	0.69

* Plus–minus values are means ± SD. To convert the value for creatinine to micromoles per liter, multiply by 88.4. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve replacement.

† The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher numbers indicating greater risk. An STS score higher than 10% indicates very high surgical risk.

¶ Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

Table 2: COHORT B – Baseline Characteristics of the Patients and Echocardiographic Findings* (ITT Population)			
Characteristic	**TAVR (N = 179)**	**Control Group (N = 179)**	**P Value**
Age – yr	83.1 ± 8.6	83.2 ± 8.3	0.95
Male sex – no. (%)	82 (45.8)	84 (46.9)	0.92
STS score†	11.2 ± 5.8	11.9 ± 4.8	0.14
NYHA class – no. (%):			0.68
II	14 (7.8)	11 (6.1)	
III or IV	165 (92.2)	168 (93.9)	
Coronary artery disease – no. (%)	121 (67.6)	133 (74.3)	0.20
Previous myocardial infarction – no./total no. (%)	33/177 (18.6)	47/179 (26.3)	0.10
Previous intervention – no./total no. (%):			
CABG	58/179 (32.4)	73/179 (40.8)	0.12
PCI	47/179 (26.3)	39/179 (21.8)	0.39
Balloon aortic valvuloplasty	25/154 (16.2)	39/160 (24.4)	0.09
Cerebral vascular disease – no./total no. (%)	48/175 (27.4)	46/171 (26.9)	1.00
Peripheral vascular disease – no./total no. (%)	55/178 (30.9)	45/179 (25.1)	0.24
COPD – no. (%):			
Any	74 (41.3)	94 (52.5)	0.04
Oxygen-dependent	38 (21.2)	46 (25.7)	0.38
Creatinine > 2 mg/dL (177 µmol/liter) – no./total no. (%)	8/179 (4.5)	16/178 (9.0)	0.10
Atrial fibrillation – no./total no. (%)	28/85 (32.9)	39/80 (48.8)	0.04
Permanent pacemaker – no./total no. (%)	35/179 (19.6)	31/179 (17.3)	0.68
Pulmonary hypertension – no./total no. (%)	50/118 (42.4)	53/121 (43.8)	0.90
Extensively calcified aorta – no. (%)	34 (19.0)	20 (11.2)	0.05
Deleterious effects of chest-wall irradiation – no. (%)	16 (8.9)	15 (8.4)	1.00
Chest-wall deformity – no. (%)	15 (8.4)	9 (5.0)	0.29
Liver disease – no./total no. (%)	6/177 (3.4)	6/178 (3.4)	1.00
Echocardiographic findings:			
Aortic-valve area – cm^2	0.6 ± 0.2	0.6 ± 0.2	0.97
Mean aortic-valve gradient – mmHg	44.5 ± 15.7	43.0 ± 15.3	0.39
Mean LVEF – %	53.9 ± 13.1	51.1 ± 14.3	0.06
Moderate or severe mitral regurgitation – no./total no. (%)¶	38/171 (22.2)	38/165 (23.0)	0.90

* Plus–minus values are means ± SD. To convert the value for creatinine to micromoles per liter, multiply by 88.4. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve replacement.

† The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher numbers indicating greater risk. An STS score higher than 10% indicates very high surgical risk.

¶ Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

Table 3: COHORT A – Procedure Data (AT Population)			
	TA TAVR	TF TAVR	Pooled AVR
Variable	**Mean or % of patients (min-max)**		
Total time of procedure (min)	225 (93-595)	246 (84-624)	333 (70-750)
Skin to skin time (min)	114	142	230 (169-295)
Fluoroscopy time (min)	35	30	N/A
Volume of contrast (ml)	104	148	N/A
Use of CPB	8.8%	2.1%	100%
Use of general anesthesia	100%	100%	100%
# of devices used			
0	2.9%	4.6%	N/A
1	89.2%	90.8%	100%
2	6.9%	4.2%	N/A
3	1.0%	0.4%	N/A
Valve-in-valve procedure	1.0%	0.4%	N/A
Emergent operation due to device or procedure	1.0%	1.3%	3.8%
Valve Size			
19 mm	N/A	N/A	11.9%
21 mm	N/A	N/A	39.7%
22 mm	N/A	N/A	0.3%
23 mm	51.5%	46.8%	34.9%
25 mm	N/A	N/A	11.9%
26 mm	48.5%	53.3%	N/A
27 mm	N/A	N/A	1.0%
29 mm	N/A	N/A	0.3%
Adverse event during procedure	19.6%	21.3%	14.7%
Device malfunction	2.0%	1.3%	N/A
Device Success (deployment, AVA > 0.9, AI < 3+, 1 valve)	84.5%	80.4%	N/A
Procedure Success (Device success, no MACCE < 30d)	75.3%	76.0%	N/A

Table 4: COHORT B – TAVR Procedure Data	
Variable	**Mean or % of patients (min-max)**
Total time of procedure (min)	262 (139-616)
Skin to skin time (min)	150 (34-553)
Fluoroscopy time (min)	29 (10-68)
Volume of contrast (ml)	132 (10-450)
Use of CPB	1.1%
Use of general anesthesia	100%
# of devices used	
0	4.6%
1	89.1%
2	5.7%
3	0.6%
Valve-in-valve procedure	2.3%
Emergent operation due to device or procedure	1.1%
Valve Size	
23 mm	56.6%
26 mm	43.4%
Adverse event during procedure	39.4%
Device malfunction	3.4%
Device Success (deployment, AVA > 0.9, AI < 3+, 1 valve)	78.2%
Procedure Success (Device success, no MACCE < 30d)	71.8%

Table 5: COHORT A – Clinical Outcomes of the Pooled TAVR and Pooled AVR Groups up to 2 Years (AT Population)												
	30 Days				31 Days-1 Year				1 Year-2 Years			
Outcome	Pooled TAVR (N = 344)	KM Event rate TAVR*	Pooled AVR (N = 313)	KM Event rate AVR	Pooled TAVR (N = 344)	KM Event rate TAVR*	Pooled AVR (N = 313)	KM Event rate AVR	Pooled TAVR (N = 344)	KM Event rate TAVR*	Pooled AVR (N = 313)	KM Event rate AVR
Death	18	5.2%	25	8.0%	63	23.7%	53	25.2%	33	33.9%	21	32.7%
Death from cardiovascular cause[a]	14	4.1%	9	2.9%	30	13.6%	24	11.5%	20	20.8%	16	18.5%
Repeat hospitalization[b]	18	5.4%	18	6.1%	40	17.3%	29	16.6%	15	23.8%	9	20.8%
Death from any cause or repeat hospitalization[b]	35	10.2%	43	13.8%	86	33.9%	74	35.5%	48	46.2%	33	44.4%
TIA[d]	3	0.9%	1	0.3%	5	2.7%	3	1.5%	2	3.6%	2	2.7%
All Stroke[c]	15	4.4%	8	2.6%	4	5.8%	1	3.0%	4	7.5%	3	4.4%
Myocardial Infarction[g]												
All	0	0.0%	1	0.3%	0	0.0%	0	0.3%	2	0.0%	0	1.3%
Peri-procedural	0	0.0%	1	0.3%	0	0.0%	0	0.3%	0	0.0%	0	0.3%
Aortic Insufficiency												
Mild	138	42.1%	34	11.9%	105	60.3%	18	16.4%	38	62.7%	8	17.8%
Moderate or greater	43	13.2%	4	1.4%	21	17.4%	4	2.7%	8	19.9%	1	2.7%
Hemorrhagic Vascular Complication[f]	84	24.5%	87	27.8%	10	26.8%	3	28.6%	3	28.0%	2	29.4%
Major Vascular Complication[i]	38	11.1%	12	3.8%	0	11.1%	0	3.8%	1	11.4%	0	3.8%
Renal Failure[h]	13	3.8%	14	4.6%	4	5.2%	5	6.5%	2	6.0%	0	6.5%
Renal Insufficiency	19	5.6%	18	5.8%	3	6.6%	7	7.8%	4	8.1%	1	8.3%
Bleeding Event[e]	35	10.2%	89	28.4%	0	10.2%	0	28.4%	0	10.2%	0	28.4%
Cardiac reintervention												
Balloon aortic valvuloplasty	0	N/A	0	N/A	2	N/A	0	N/A	0	N/A	0	N/A
Repeat TAVR	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Aortic-valve replacement	7	N/A	0	N/A	1	N/A	0	N/A	1	N/A	0	N/A
Endocarditis	0	0.0%	1	0.3%	3	1.0%	2	1.1%	1	1.5%	0	1.1%
New pacemaker	16	4.7%	14	4.6%	4	6.1%	2	5.3%	2	6.9%	3	6.8%

*Kaplan-Meier event rates are reported at 30 days, one year, and two years.
N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.
Data presented as n (%) of patients unless otherwise specified.
a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.
d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.
e. Bleeding event is defined as ≥ 2 units within the index procedure.
f. Hemorrhagic vascular complications are defined as a hematoma at the access site > 5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index procedure was reported as a serious adverse event.
g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non-Q-wave MI.
h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).
i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.

Table 6: COHORT A – Clinical Outcomes in the Transfemoral Group up to 2 Years (AT Population)

Outcome	30 Days				31 Days-1 Year				1 Year-2 Years			
	TF TAVR (N = 240)	KM Event rate TAVR*	AVR (N = 221)	KM Event rate AVR	TF TAVR (N = 240)	KM Event rate TAVR*	AVR (N = 221)	KM Event rate AVR	TF TAVR (N = 240)	KM Event rate TAVR*	AVR (N = 221)	KM Event rate AVR
Death	9	3.7%	18	8.2%	42	21.4%	37	25.2%	21	30.7%	13	31.6%
Death from cardiovascular cause[a]	8	3.3%	7	3.2%	19	12.0%	17	11.8%	14	19.0%	9	17.3%
Repeat hospitalization[b]	13	5.5%	12	5.8%	29	17.6%	22	17.3%	8	22.4%	4	19.8%
Death from any cause or repeat hospitalization[b]	21	8.7%	30	13.6%	59	31.8%	52	35.3%	31	42.2%	18	42.2%
TIA[d]	3	1.3%	0	0.0%	2	2.3%	1	0.6%	1	2.8%	1	1.4%
All Stroke[c]	8	3.3%	3	1.4%	1	3.8%	0	1.4%	2	5.0%	1	2.0%
Myocardial Infarction[g]												
All	0	0.0%	1	0.5%	0	0.0%	0	0.5%	0	0.0%	1	1.1%
Peri-procedural	0	0.0%	1	0.5%	0	0.0%	0	0.5%	0	0.0%	0	0.5%
Aortic Insufficiency												
Mild	105	45.5%	24	11.9%	84	65.9%	12	16.3%	32	68.2%	5	17.3%
Moderate or greater	38	16.5%	2	1.0%	19	21.8%	3	2.8%	7	25.1%	1	2.8%
Hemorrhagic Vascular Complication[f]	69	28.8%	61	27.6%	5	30.2%	2	28.7%	1	30.7%	2	29.8%
Major Vascular Complication[i]	34	14.2%	7	3.2%	0	14.2%	0	3.2%	1	14.7%	0	3.2%
Renal Failure[h]	8	3.4%	7	3.2%	3	4.7%	4	5.5%	2	5.8%	0	5.5%
Renal Insufficiency	7	2.9%	13	6.0%	2	3.9%	6	8.2%	4	5.9%	0	8.2%
Bleeding Event[e]	27	11.3%	63	28.5%	0	11.3%	0	28.5%	0	11.3%	0	28.5%
Cardiac reintervention												
Balloon aortic valvuloplasty	0	N/A	0	N/A	2	N/A	0	N/A	0	N/A	0	N/A
Repeat TAVR	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Aortic-valve replacement	4	N/A	0	N/A	1	N/A	0	N/A	1	N/A	0	N/A
Endocarditis	0	0.0%	0	0.0%	2	1.0%	2	1.1%	1	1.6%	0	1.1%
New pacemaker	11	4.6%	9	4.2%	3	6.0%	0	4.2%	2	7.2%	3	6.2%

*Kaplan-Meier event rates are reported at 30 days, one year, and two years.

N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.

Data presented as n (%) of patients unless otherwise specified.

a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.

b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).

c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.

d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.

e. Bleeding event is defined as ≥ 2 units within the index procedure.

f. Hemorrhagic vascular complications are defined as a hematoma at the access site > 5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index procedure was reported as a serious adverse event.

g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non-Q-wave MI.

h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).

i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.

Table 7: COHORT A – Clinical Outcomes in the Transapical Group up to 2 Years (AT Population)

Outcome	30 Days				31 Days-1 Year				1 Year-2 Years			
	TA TAVR (N = 104)	KM Event rate TAVR*	AVR (N = 92)	KM Event rate AVR	TA TAVR (N = 104)	KM Event rate TAVR*	AVR (N = 92)	KM Event rate AVR	TA TAVR (N = 104)	KM Event rate TAVR*	AVR (N = 92)	KM Event rate AVR
Death	9	8.7%	7	7.6%	21	29.1%	16	25.3%	12	41.3%	8	35.5%
Death from cardiovascular cause[a]	6	5.8%	2	2.2%	11	17.4%	7	10.8%	6	25.2%	7	21.6%
Repeat hospitalization[b]	5	5.1%	6	6.8%	11	16.7%	7	14.9%	7	27.4%	5	23.3%
Death from any cause or repeat hospitalization[b]	14	13.5%	13	14.1%	27	38.7%	22	36.3%	17	55.3%	15	49.6%
TIA[d]	0	0.0%	1	1.1%	3	3.7%	2	3.9%	1	5.8%	1	5.6%
All Stroke[c]	7	7.0%	5	5.5%	3	10.8%	1	7.0%	2	13.8%	2	10.0%
Myocardial Infarction[g]												
All	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.5%
Peri-procedural	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Aortic Insufficiency												
Mild	33	34.0%	10	11.8%	21	45.8%	6	16.4%	6	48.1%	3	19.4%
Moderate or greater	5	5.3%	2	2.4%	2	6.6%	1	2.4%	1	6.6%	0	2.4%
Hemorrhagic Vascular Complication[f]	15	14.5%	26	28.3%	5	19.2%	1	28.3%	2	22.0%	0	28.3%
Major Vascular Complication[i]	4	3.9%	5	5.4%	0	3.9%	0	5.4%	0	3.9%	0	5.4%
Renal Failure[h]	5	5.0%	7	7.7%	1	6.2%	1	8.9%	0	6.2%	0	8.9%
Renal Insufficiency	12	11.9%	5	5.5%	1	13.1%	1	6.9%	0	13.1%	1	8.4%
Bleeding Event[e]	8	7.7%	26	28.3%	0	7.7%	0	28.3%	0	7.7%	0	28.3%
Cardiac reintervention												
Balloon aortic valvuloplasty	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Repeat TAVR	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Aortic-valve replacement	3	N/A	0	N/A	0	N/A	0	N/A	0	N/A	0	N/A
Endocarditis	0	0.0%	1	1.1%	1	1.2%	0	1.1%	0	1.2%	0	1.1%
New pacemaker	5	5.0%	5	5.6%	1	6.2%	2	8.1%	0	6.2%	0	8.1%

*Kaplan-Meier event rates are reported at 30 days, one year, and two years.

N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.

Data presented as n (%) of patients unless otherwise specified.

a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.

b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).

c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.

d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.

e. Bleeding event is defined as ≥ 2 units within the index procedure.

f. Hemorrhagic vascular complications are defined as a hematoma at the access site > 5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index procedure was reported as a serious adverse event.

g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non-Q-wave MI.

h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).

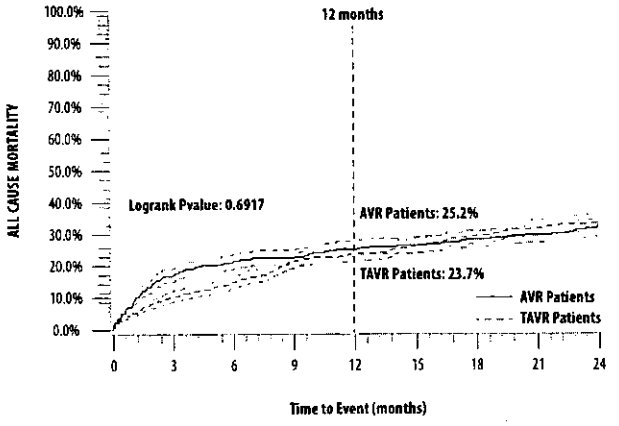
i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.

Table 8: COHORT B – Clinical Outcomes up to 2 Years (ITT Population)												
	30 Days				31 Days-1 Year				1 Year-2 Years			
Outcome	TAVR (N = 179)	KM Event rate*	Control Group (N = 179)	KM Event rate	TAVR (N = 179)	KM Event rate*	Control Group (N = 179)	KM Event rate	TAVR (N = 179)	KM Event rate*	Control Group (N = 179)	KM Event rate
Death from any cause	9	5.0%	5	2.8%	46	30.7%	84	50.7%	22	43.3%	28	68.0%
Death from cardiovascular cause[a]	8	4.5%	3	1.7%	27	20.5%	72	44.6%	15	31.0%	25	62.4%
Repeat hospitalization[b]	12	6.9%	18	10.2%	35	27.0%	70	53.9%	15	35.0%	24	72.5%
Death from any cause or repeat hospitalization[b]	21	11.7%	22	12.3%	62	44.1%	117	71.6%	31	56.7%	45	87.9%
TIA[d]	0	0.0%	0	0.0%	1	0.7%	0	0.0%	2	2.5%	0	0.0%
All Stroke[c]	13	7.3%	3	1.7%	6	11.2%	5	5.5%	3	13.8%	0	5.5%
Myocardial Infarction[g]												
All	0	0.0%	0	0.0%	1	0.8%	1	0.7%	1	1.6%	1	2.5%
Peri-procedural	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Aortic Insufficiency												
Mild	89	53.3%	59	34.1%	49	66.2%	21	47.3%	24	70.7%	9	49.6%
Moderate or greater	23	13.9%	21	12.1%	15	19.4%	9	16.8%	4	22.0%	3	19.0%
Hemorrhagic Vascular Complication[f]	46	25.8%	10	5.7%	16	34.3%	16	17.7%	8	39.8%	5	22.9%
Major Vascular Complication[i]	30	16.8%	2	1.1%	2	17.4%	2	2.8%	0	17.4%	0	2.8%
Renal Failure[h]	2	1.1%	3	1.7%	2	2.3%	4	4.7%	1	3.2%	3	7.6%
Renal Insufficiency	8	4.6%	1	0.6%	4	7.3%	5	4.2%	3	9.9%	4	9.6%
Bleeding Events[e]	29	16.2%	4	2.2%	2	17.3%	0	2.2%	0	17.3%	0	2.2%
Cardiac reintervention												
Balloon aortic valvuloplasty	3	1.7%	11	6.1%	0	1.7%	41	29.1%	2	3.4%	7	33.0%
Repeat TAVR[e]	3	N/A	N/A	N/A	0	N/A	N/A	N/A	0	N/A	N/A	N/A
Aortic-valve replacement	0	0.0%	4	2.3%	0	0.0%	6	7.6%	1	0.9%	1	8.9%
Endocarditis	0	0.0%	0	0.0%	2	1.4%	1	0.8%	1	2.3%	0	0.8%
New pacemaker	6	3.4%	9	5.1%	2	4.7%	5	8.6%	2	6.4%	0	8.6%

*Kaplan-Meier event rates are reported at 30 days, one year, and two years.
N/A = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.
Data presented as n (%) of patients unless otherwise specified.
a. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
c. Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.
d. TIA was defined as a fully reversible neurologic event that lasted less than 24 hours and if an imaging study was performed, showed no evidence of infarction.
e. Bleeding event is defined as ≥ 2 units within the index procedure.
f. Hemorrhagic vascular complications are defined as a hematoma at the access site > 5 cm, false aneurysm, arterio-venous fistula, retroperitoneal bleeding, peripheral ischemia/nerve injury, vascular surgical repair or any transfusion during or related to the index procedure. Hemorrhage that required ≥ 2 units of transfusion within the index procedure was reported as a serious adverse event.
g. Myocardial infarction was defined as an acute MI at autopsy, emergent PCI or thrombolytics for acute myocardial infarction, evidence of Q-wave MI or non-Q-wave MI.
h. Renal failure was defined as initiation of any dialysis (hemodialysis, continuous venovenous hemodialysis [CVVHD], peritoneal).
i. Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.

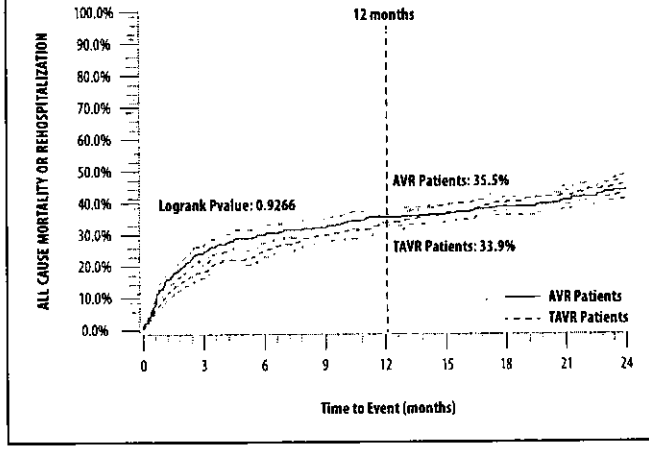
THV269

Figure 3. COHORT A - Primary Endpoint:
All Cause Mortality (AT Population)
(68% confidence limits displayed)



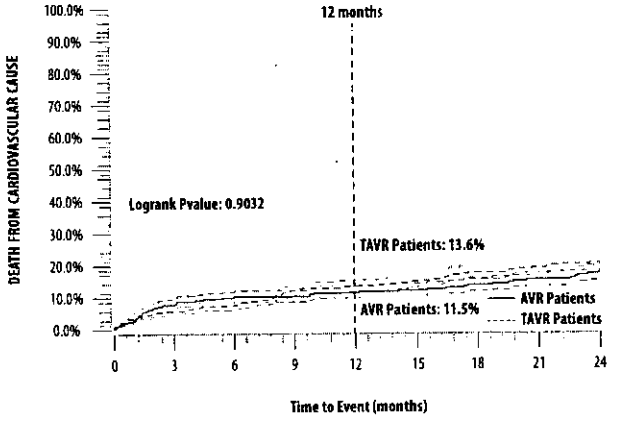
THV270

Figure 4. COHORT A - Secondary Endpoint:
Mortality or Repeat Hospitalization (AT Population)
(68% confidence limits displayed)



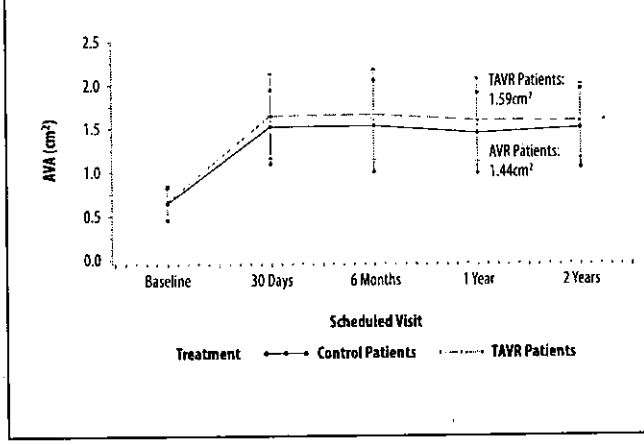
THV271

Figure 5. COHORT A - Secondary Endpoint:
Death from Cardiovascular Cause (AT Population)
(68% confidence limits displayed)



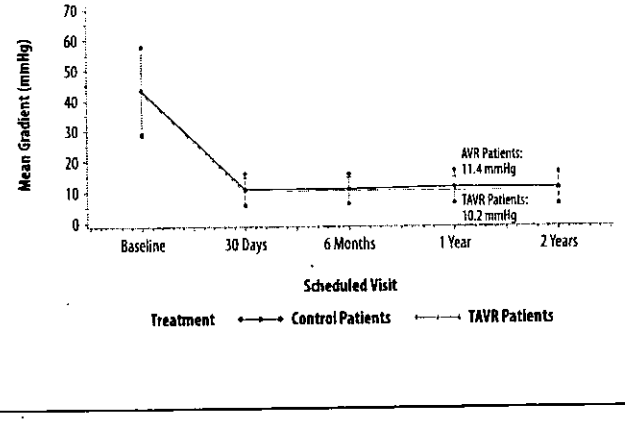
THV272

Figure 6. COHORT A - Secondary Endpoint:
AVA Over Time (AT Population)
(one standard deviation displayed)



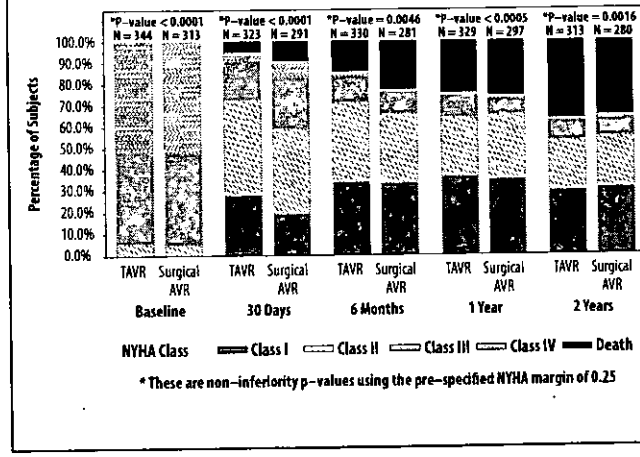
THV273

Figure 7. COHORT A - Secondary Endpoint:
Mean Gradient Over Time (AT Population)
(one standard deviation displayed)



THV274

Figure 8. COHORT A - Secondary Endpoint:
NYHA at 2 Year Visit (AT Population)



* These are non-inferiority p-values using the pre-specified NYHA margin of 0.25

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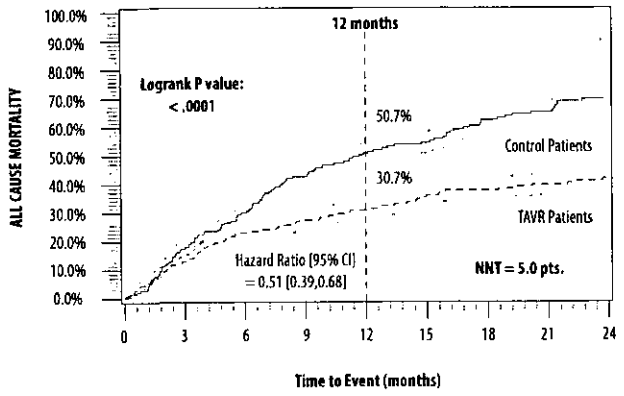
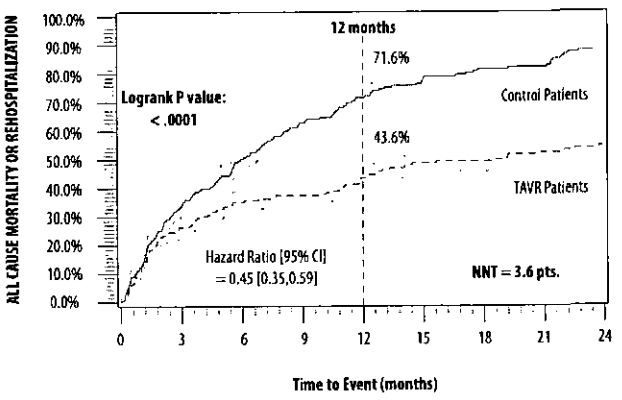
THV241

Figure 9. COHORT B - Primary Endpoint:
All Cause Mortality (ITT Population)
(68% confidence limits displayed)



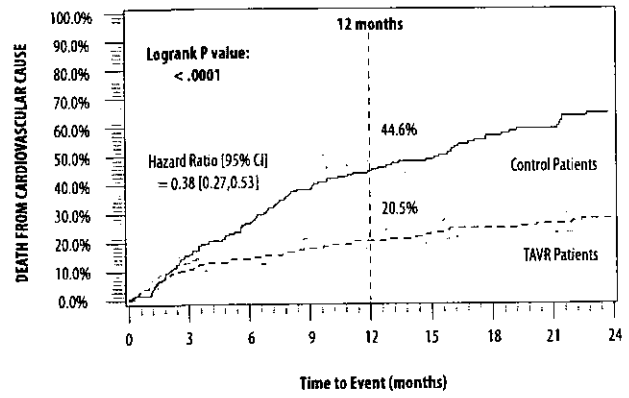
THV242

Figure 10. COHORT B - Co-Primary Endpoint:
Mortality or Repeat Hospitalization (ITT Population)
(68% confidence limits displayed)



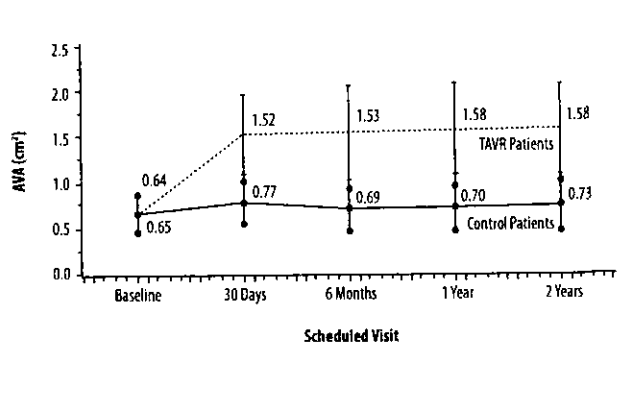
THV243

Figure 11. COHORT B - Secondary Endpoint:
Death from Cardiovascular Cause (ITT Population)
(68% confidence limits displayed)



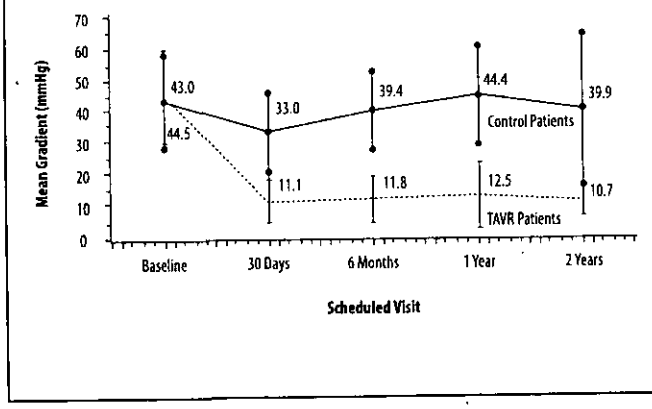
THV245

Figure 12. COHORT B - Secondary Endpoint:
AVA Over Time (ITT Population)
(one standard deviation displayed)



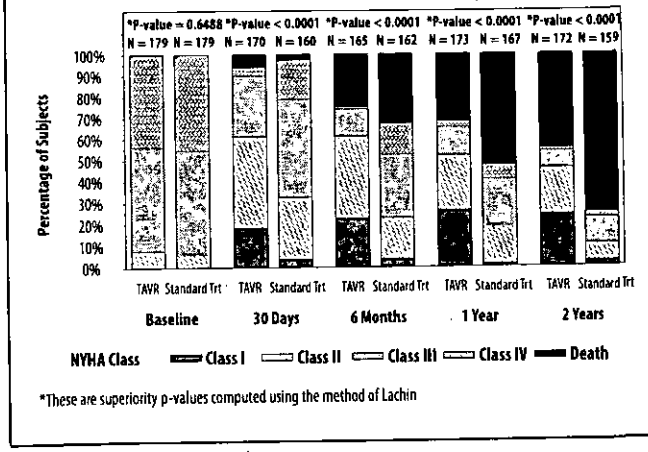
THV246

Figure 13. COHORT B - Secondary Endpoint:
Mean Gradient Over Time (ITT Population)
(one standard deviation displayed)



THV261

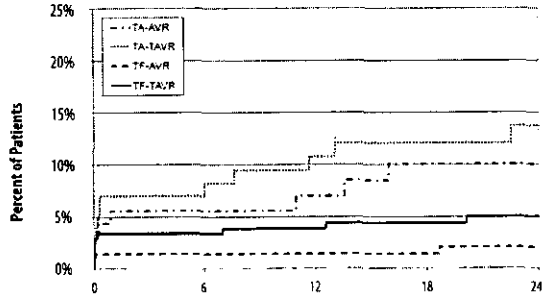
Figure 14. COHORT B - Secondary Endpoint:
NYHA at 2 Year Visit (ITT Population)



*These are superiority p-values computed using the method of Lachin

Figure 15. COHORT A - PMA Patients (AT)
Stroke Incidence

THV295



Patients at Risk		Months post Procedure			
TA-AVR	92	67	63	56	31
TA-TAVR	104	77	67	58	33
TF-AVR	221	170	160	150	108
TF-TAVR	240	204	182	165	113

Table 9: Stroke Incidence – COHORT A – PMA Patients (AT)

Months after procedure		0	6	12	18	24
TA-AVR	Patients at Risk	92	67	63	56	31
	Cumulative Incidence	1.1%	5.5%	7.0%	10.0%	10.0%
TA-TAVR	Patients at Risk	104	77	67	58	33
	Cumulative Incidence	0.0%	7.0%	10.8%	12.1%	13.8%
TF-AVR	Patients at Risk	221	170	160	150	108
	Cumulative Incidence	0.4%	1.4%	1.4%	1.4%	2.0%
TF-TAVR	Patients at Risk	240	204	182	165	113
	Cumulative Incidence	0.8%	3.4%	3.8%	4.4%	5.0%

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10/12

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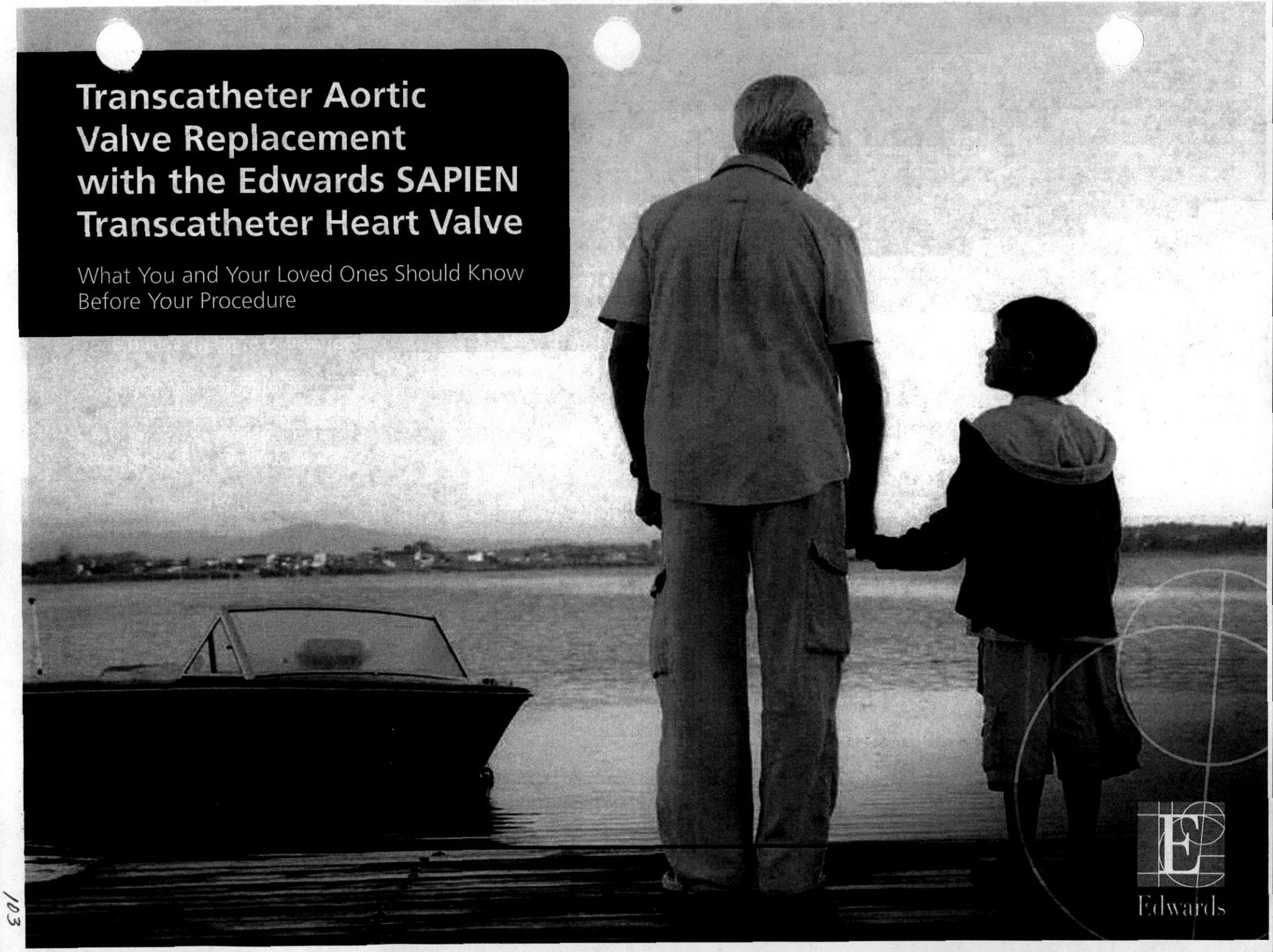
Transcatheter Aortic Valve Replacement with the Edwards SAPIEN Transcatheter Heart Valve
What You and Your Loved Ones Should Know Before Your Procedure
Edwards

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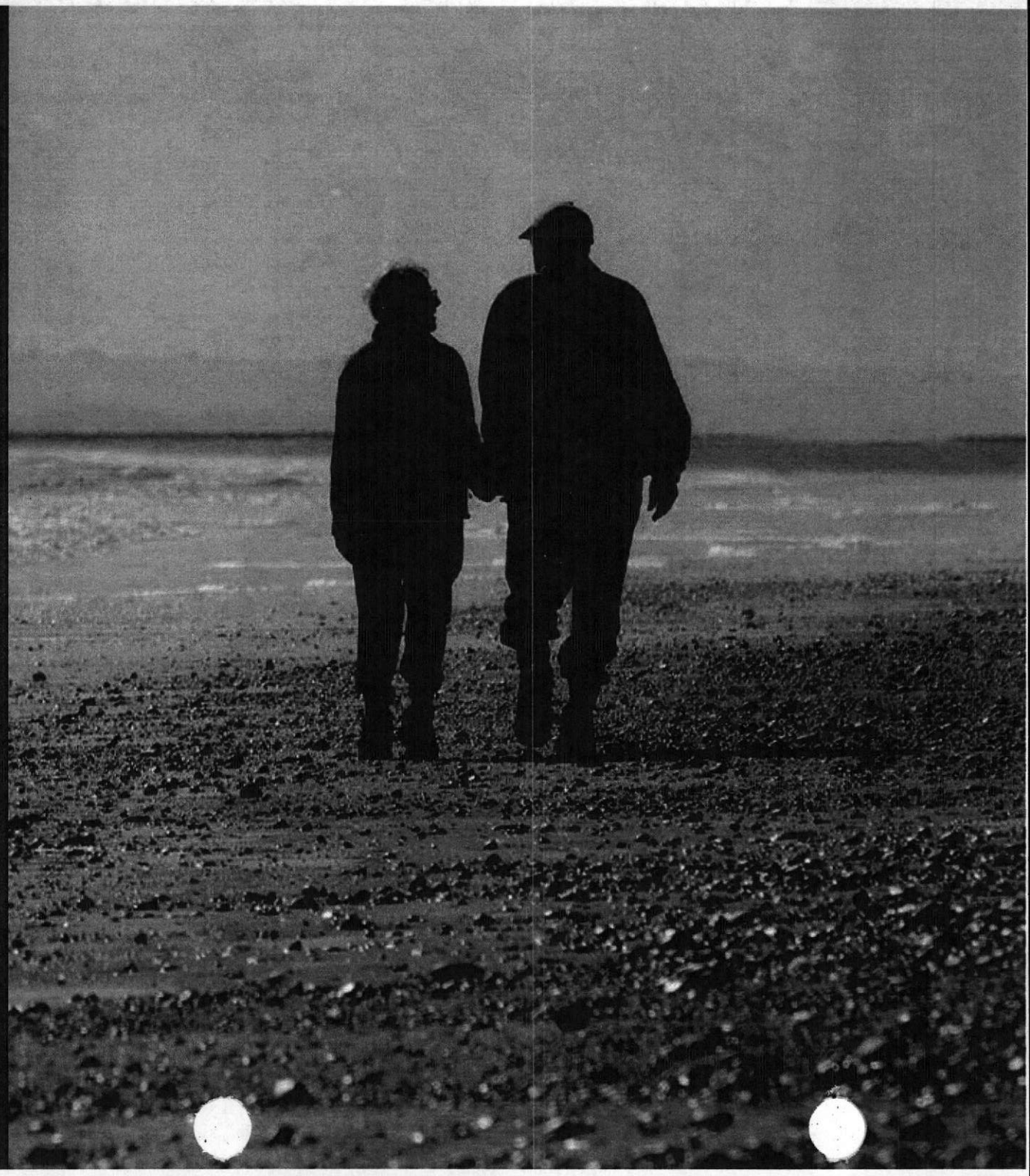
This booklet was created for patients who feel sick from severe aortic stenosis (a narrowing of the aortic valve opening that does not allow normal blood flow) and who are at high risk or cannot have open-heart surgery, in order to inform them of their options. This information will help you and your loved ones learn more about your heart, how it works, and aortic stenosis. In addition, you will learn about a new procedure called transcatheter aortic valve replacement (TAVR).

Be sure to ask your doctor to explain your treatment options, and their risks, to help you decide which option is best for you.

See pages 19-28 to review the risks of the TAVR procedure.



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Please remember, this information is not meant to tell you everything you need to know about your treatment options for aortic stenosis, or about the TAVR procedure. Regular check-ups with your doctor are essential. Call or see your doctor whenever you have questions or concerns about your health, especially if you experience unusual symptoms or changes in your overall health.

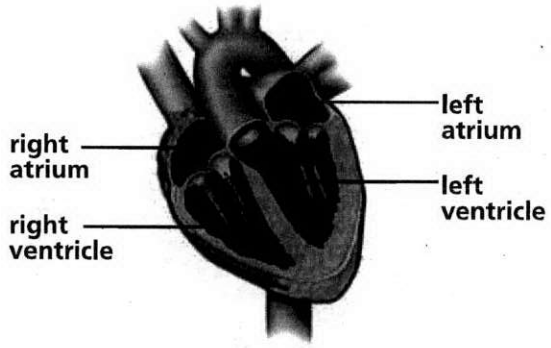
HOW DOES YOUR HEART WORK?

The heart is a muscular organ located in your chest between your lungs. The heart is designed to pump blood through your body. The right side of your heart pumps blood through the lungs, where the blood picks up oxygen. The left side of the heart receives this blood and pumps it to the rest of your body.

Your heart beats between 60 and 100 times per minute. At 60 beats per minute, that's approximately 31.5 million beats per year.

Chambers and Valves

The heart is divided into four main areas, or chambers—two upper chambers (called the left and right atrium) and two lower chambers (called the left and right ventricle). There are four valves that control the flow of blood through your heart. They are called the aortic, mitral, pulmonary, and tricuspid valves, and each is made of flaps of tissue called leaflets. *(See figure on page 4)*



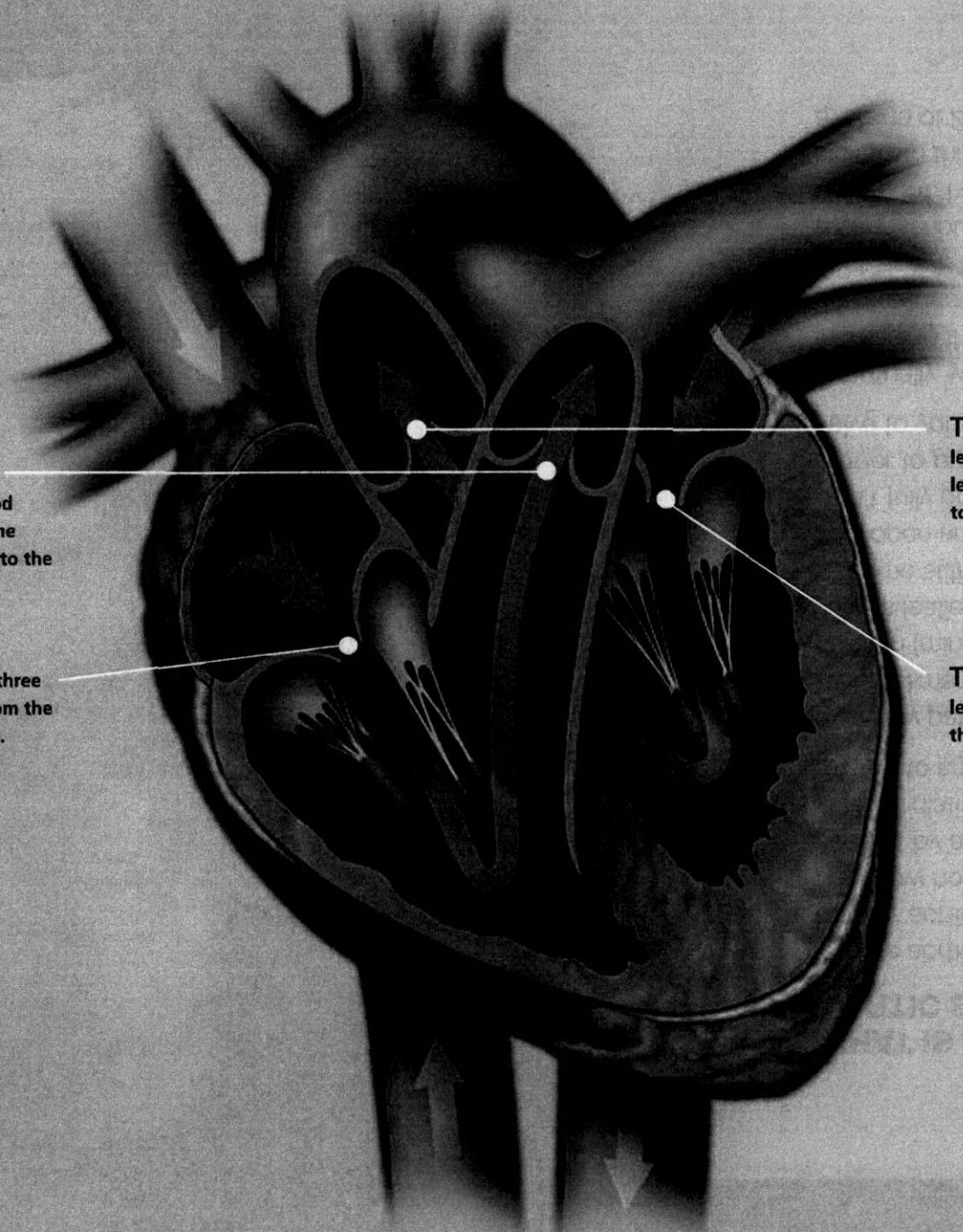
NOTE: The left and the right side of the heart is pictured as the heart sits in your body.

Each time your heart beats, it pumps blood through these valves by contracting (squeezing) its chambers. These valves open in one direction, like one-way gates, allowing blood to flow forward. In between beats, the heart's chambers quickly relax, and its valves close, preventing blood from flowing backward.

There are two common problems that can develop in heart valves:

- When your valve is narrowed and does not completely open because of things like a build-up of calcium (mineral deposits), high cholesterol (a waxy fat), age, or genetics (such as a birth defect), this is called stenosis.
- When your valve does not fully close and allows blood to leak backwards through the valve, this is called regurgitation.

With either problem, your heart needs to work harder and may not pump enough oxygen-rich blood to your body.



The pulmonary valve has three leaflets. It controls blood flow from the right ventricle to the pulmonary artery, sending blood to the lungs to pick up oxygen.

The tricuspid valve has three leaflets. It controls blood flow from the right atrium to the right ventricle.

The aortic valve has three leaflets. It controls blood flow from the left ventricle to the aorta, sending blood to the rest of the body.

The mitral valve has two leaflets. It controls blood flow between the left atrium and left ventricle.

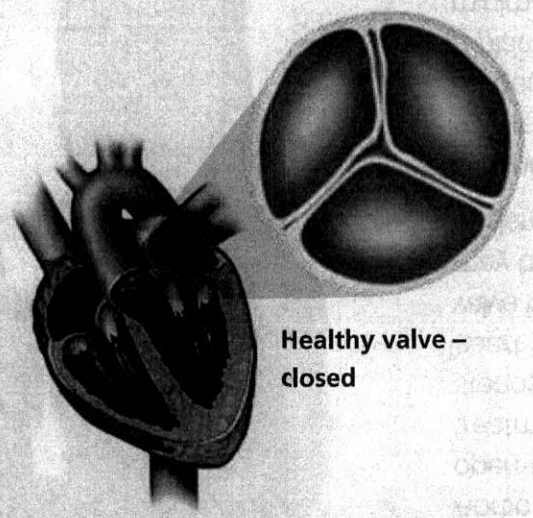
WHAT IS SEVERE AORTIC STENOSIS?

Severe aortic stenosis is a narrowing of your aortic valve opening that does not allow normal blood flow. It can be caused by a birth defect, rheumatic fever, radiation therapy, or can be related to age.

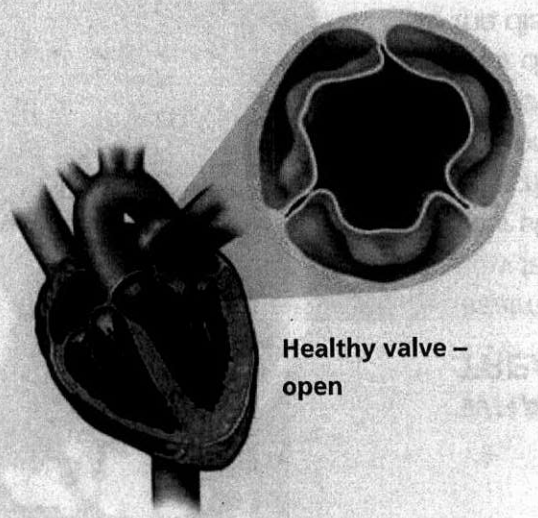
In elderly patients, severe aortic stenosis is sometimes caused by the build-up of calcium (mineral deposits) on the aortic valve's leaflets. Over time the leaflets become stiff, reducing their ability to fully open and close. When the leaflets don't fully open, your heart must work harder to push blood through the aortic valve to your body.

Eventually, your heart gets weaker, increasing the risk of heart failure (your heart cannot supply enough blood to your body). Severe aortic stenosis is a very serious problem. Without treatment, half of the people who feel sick from this problem die within an average of 2 years.

HEALTHY AORTIC VALVE

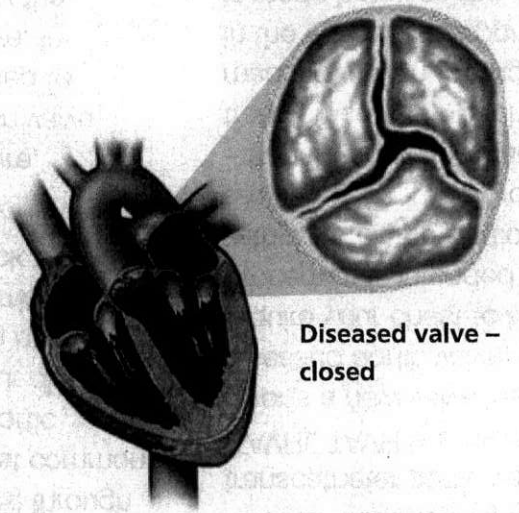


Healthy valve – closed

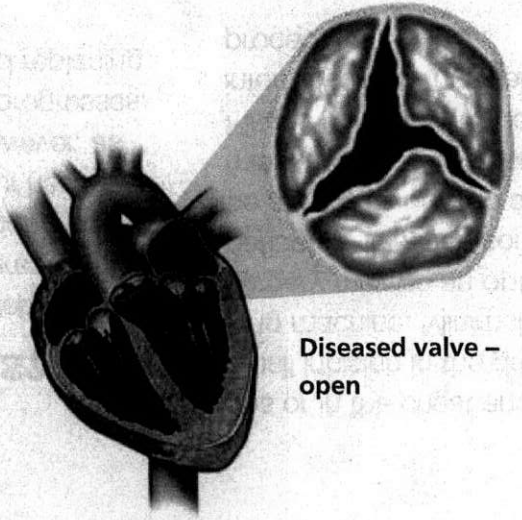


Healthy valve – open

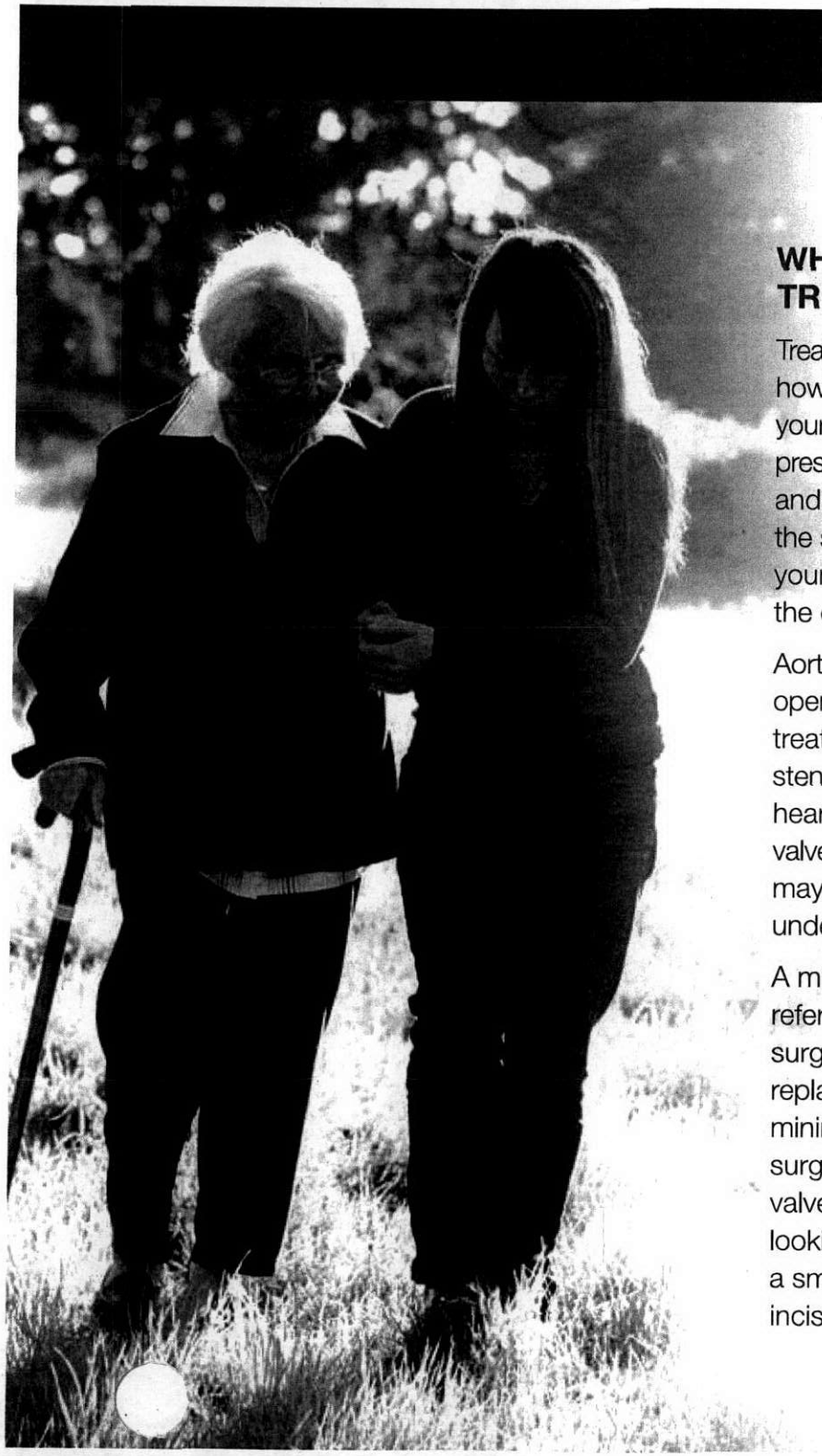
DISEASED AORTIC VALVE



Diseased valve – closed



Diseased valve – open



WHAT ARE YOUR TREATMENT OPTIONS?

Treatment for aortic stenosis depends on how far the disease has progressed. If your stenosis is mild, medication may be prescribed to help regulate your heartbeat and prevent blood clots. However, as the severity of your stenosis progresses, your doctor may recommend replacing the diseased valve.

Aortic valve replacement (AVR) through open-heart surgery is the most common treatment for patients with aortic stenosis. In this operation your diseased heart valve is removed and a new heart valve is inserted. However, some patients may be at high risk or too sick to undergo open-heart surgery.

A minimally invasive procedure, referred to as minimal incision valve surgery, can also be performed to replace a malfunctioning valve. In minimal incision valve surgery the surgeon can replace the diseased valve through a smaller incision while looking directly at the heart or through a small, tube-shaped camera. The incisions are made either between the ribs or in the chest and may use a small incision in the groin for the heart lung machine. Minimal incision valve surgery may be an option for some patients. However, some patients may be at high risk or too sick to undergo minimally invasive open-heart surgery. Please consult your doctor for more information on minimally invasive procedures.

Another treatment option is transcatheter aortic valve replacement (TAVR). TAVR is a procedure that inserts a new valve inside your diseased aortic valve, and does not require your chest to be opened. This procedure is intended only for patients with age-related aortic stenosis. There are two different approaches for TAVR – transfemoral and transapical. In the transfemoral approach, an incision is made in the leg (or slightly higher up). In the transapical approach, an incision is made between the ribs to access the apex (lowest point) of the heart. Your doctor will recommend the best treatment option for you based on your overall health. If you are too sick to undergo chest surgery, the transapical approach may not be an option for you.

What is Surgical Aortic Valve Replacement?

Surgical AVR is an open-heart procedure. After the chest is opened, you are put on cardiopulmonary bypass – which temporarily takes over providing blood flow and oxygen to your body during surgery. During surgical AVR, the surgeon removes the diseased aortic valve and replaces it with either a mechanical valve (made from man-made materials) or a biological valve (made from animal tissue). Surgical AVR has been performed for many years and has consistently produced excellent results in lengthening patients' lives and improving their quality of life.

What is Transcatheter Aortic Valve Replacement?

If a cardiac surgeon determines that you are at high risk or too sick for open-heart surgery, and if medicine is not helping you feel better, TAVR may be an alternative. This less invasive procedure allows a new valve to be inserted within your diseased aortic valve while your heart is still beating. Cardiopulmonary bypass is usually not required. However, during parts of the procedure your heart rate needs to be temporarily increased to a very fast rate resulting in lower than normal blood flow to vital organs for short periods of time. The TAVR procedure can be performed through two different approaches – transfemoral or transapical. Your doctor will decide which approach is best for you based on your medical condition and other factors.

The TAVR procedure is not right for everyone. In certain cases, the risks of the procedure may outweigh the benefits. See pages 19-28 to review the risks of the TAVR procedure.

	Surgical AVR	Transfemoral TAVR	Transapical TAVR
Anesthesia	General	General	General
Cardiopulmonary bypass	Required	Usually not required	Usually not required
Pacing (temporarily increasing your heart rate during the procedure)	Not required	Required	Required
Entry site	Incision in chest	Incision in leg (or slightly higher up)	Incision in chest between ribs
Average total procedure duration*	5-6 hours	4-5 hours	3-4 hours
Average hospital stay	14-15 days	8-9 days	12-13 days
Radiation exposure through X-ray	No	Yes	Yes
Radiographic contrast media	No	Yes	Yes

* The time required to perform the procedures necessary for the entire procedure

TRANSCATHETER AORTIC VALVE REPLACEMENT PROCEDURE

Who Should Not Have the Procedure?

The Edwards SAPIEN transcatheter heart valve should not be used in the following:

- Patients who have other such serious illnesses that they would not benefit from isolated correction of their aortic stenosis
- Patients whose aortic valve is not calcified
- Patients whose aortic valve only has one or two leaflets (usually due to a birth defect)
- Patients who have coronary artery disease that needs to be treated
- Patients who have a blood clot or an abnormal growth
- Patients who have an infection in the heart or infections elsewhere
- Patients who already have a prosthetic (man-made) valve or repair device implanted in any of their four heart valves
- Patients who have aortic stenosis along with aortic regurgitation (when your valve does not fully close and allows blood to leak backwards through the valve)
- Patients who have severe disease with their mitral valve
- Patients whose aortic valve is either too small or too big
- Patients who have severe disease in their vessels leading to the heart, small vessels, or vessels that have a lot of bends that would not allow passage of the products necessary to perform the procedure
- Patients who have thick aortic leaflets which are very close to the arteries that supply the heart with blood
- Patients who have severe problems with bleeding or blood clotting
- Patients who have a condition in which the heart muscle becomes thick
- Patients who cannot take aspirin, heparin, ticlopidine (Ticlid), clopidogrel (Plavix), or have sensitivity to contrast medium (fluid used to see your internal structures during the procedure)

If the Edwards SAPIEN transcatheter heart valve is used in the patients mentioned above, it may not work properly. This could make you feel very sick, or even cause death.

What is Surgical Aortic Valve Replacement?

Surgical AVR is an open-heart procedure. After the chest is opened, you are put on cardiopulmonary bypass – which temporarily takes over providing blood flow and oxygen to your body during surgery. During surgical AVR, the surgeon removes the diseased aortic valve and replaces it with either a mechanical valve (made from man-made materials) or a biological valve (made from animal tissue). Surgical AVR has been performed for many years and has consistently produced excellent results in lengthening patients' lives and improving their quality of life.

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Entry site	Incision in chest	Incision in leg (or slightly higher up)	Incision in chest between ribs
Average total procedure duration*	5-6 hours	4-5 hours	3-4 hours
Average hospital stay	14-15 days	8-9 days	12-13 days
Radiation exposure through X-ray	No	Yes	Yes
Radiographic contrast media	No	Yes	Yes

* The time required to perform the procedures necessary for the entire procedure

Which Products Will Be Used During the Procedure?

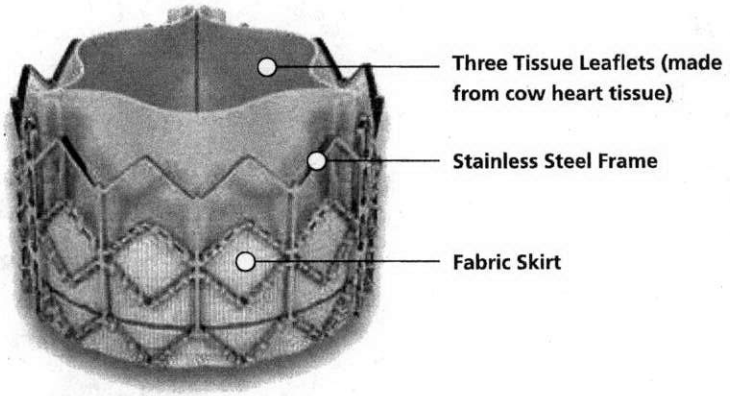
The Edwards SAPIEN transcatheter heart valve and other accessories are used to perform the TAVR procedure. The Edwards SAPIEN transcatheter heart valve is a biological (made from animal tissue) valve that replaces your aortic valve. It is provided in two sizes, 23 mm and 26 mm in diameter. Your doctor will determine the right size for you.

What Do You Need to Do Before the Procedure?

Be sure to tell your doctor what medicine you are taking and whether you have any allergies. Your doctor may ask you to change the medicine you are on before the procedure. Your doctor will also explain the procedure and answer any questions you may have.

The Edwards SAPIEN transcatheter heart valve (that replaces your diseased aortic valve) is pictured to the right.

Image is larger than actual valve size.



What Will Happen During the Procedure?

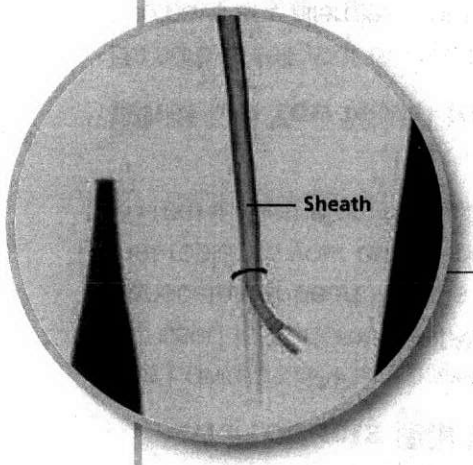
The procedure will be performed in the hospital. General anesthesia will be given to put you into a deep sleep. After you are asleep, a tube will be placed down your throat and connected to a mechanical ventilator (a machine that will help you breathe during the procedure).

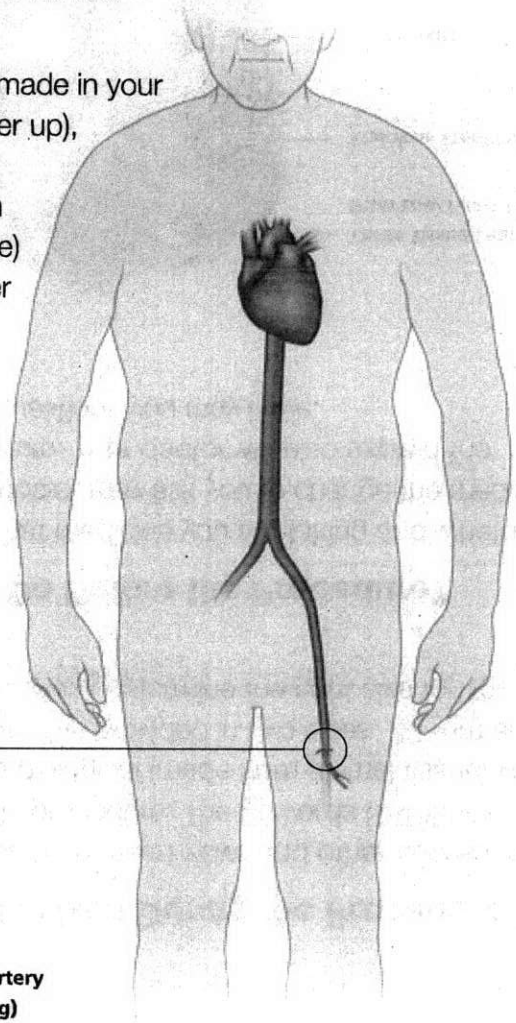
Your heart's pumping function will be briefly suspended at least twice during the procedure. To do this, your doctor will place a temporary pacing wire in your heart which causes the heart to race. This prevents your heart from pumping blood through your body well, which may result in low blood flow to your brain, kidneys, and other organs for a few seconds. After the procedure is done, the temporary pacing wire is removed.

Your doctor will use fluoroscopy (a type of X-ray that delivers radiation to you) during the procedure. Your doctor will explain the risks of radiation to you. Your doctor will also use contrast medium (fluid used to see your internal structures) during the procedure in order to see your aortic valve. Some patients may have kidney problems or an allergic reaction as a result of the contrast medium. Your doctor will also use echocardiography (a type of ultrasound) to see your aortic valve.

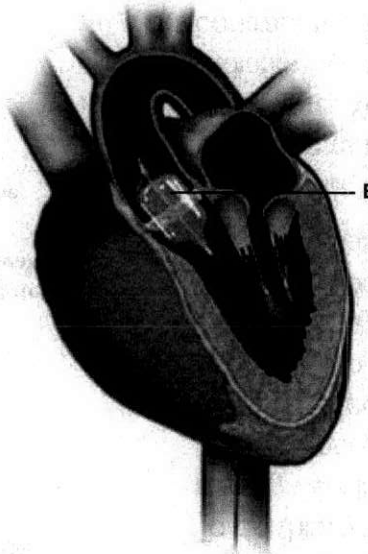
Transfemoral Procedure *The average time required to perform the transfemoral TAVR procedure is between 4 and 5 hours.*

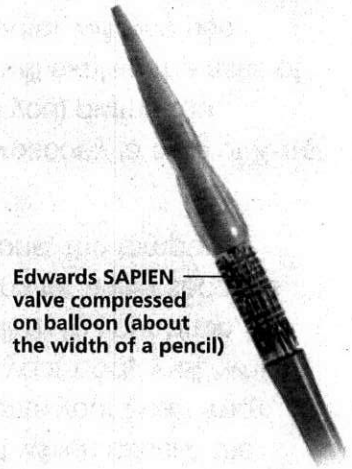
1. You will be placed under general anesthesia (you will be in a deep sleep).
2. An incision will be made in your leg (or slightly higher up), where your doctor will put in a sheath (a short hollow tube) that is slightly larger than the width of a pencil.





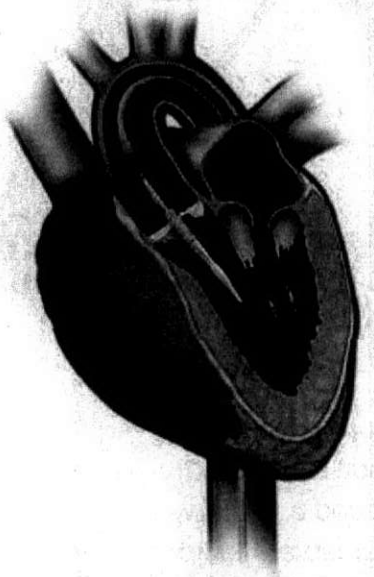
Sheath is placed in femoral artery (large artery in your upper leg)



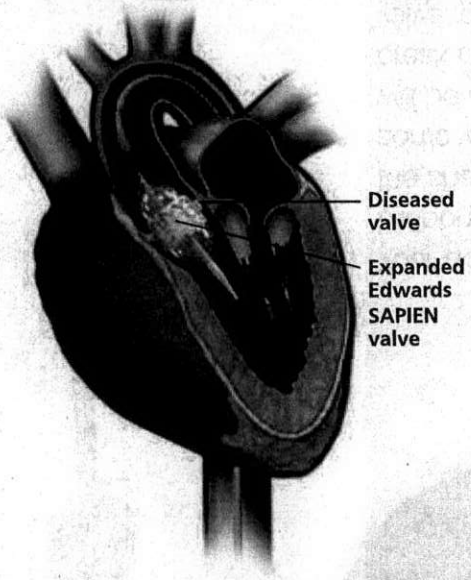


3. Your doctor will take a balloon and put it through the sheath into your blood vessel to reach your aortic valve. The balloon will be inflated with fluid to break open your narrowed valve, deflated, and then removed.

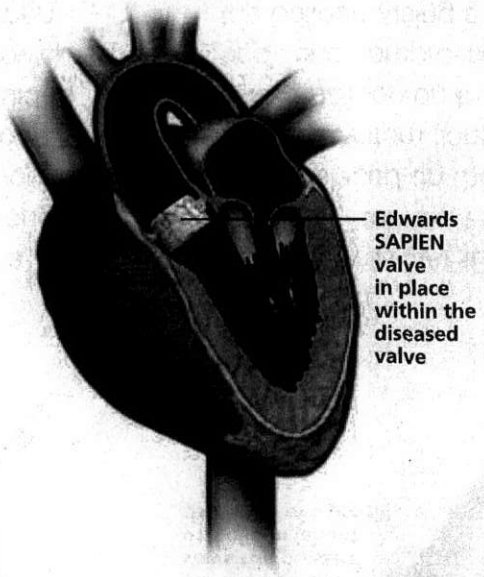
4. The Edwards SAPIEN transcatheter heart valve will be placed on the delivery system (long tube with a balloon on the end), and compressed on the balloon (using a crimper) to make it small enough to fit through the sheath. It will be about the width of a pencil.



5. The delivery system carrying the valve will be placed through the sheath and pushed up to your aortic valve, guided by a type of X-ray.



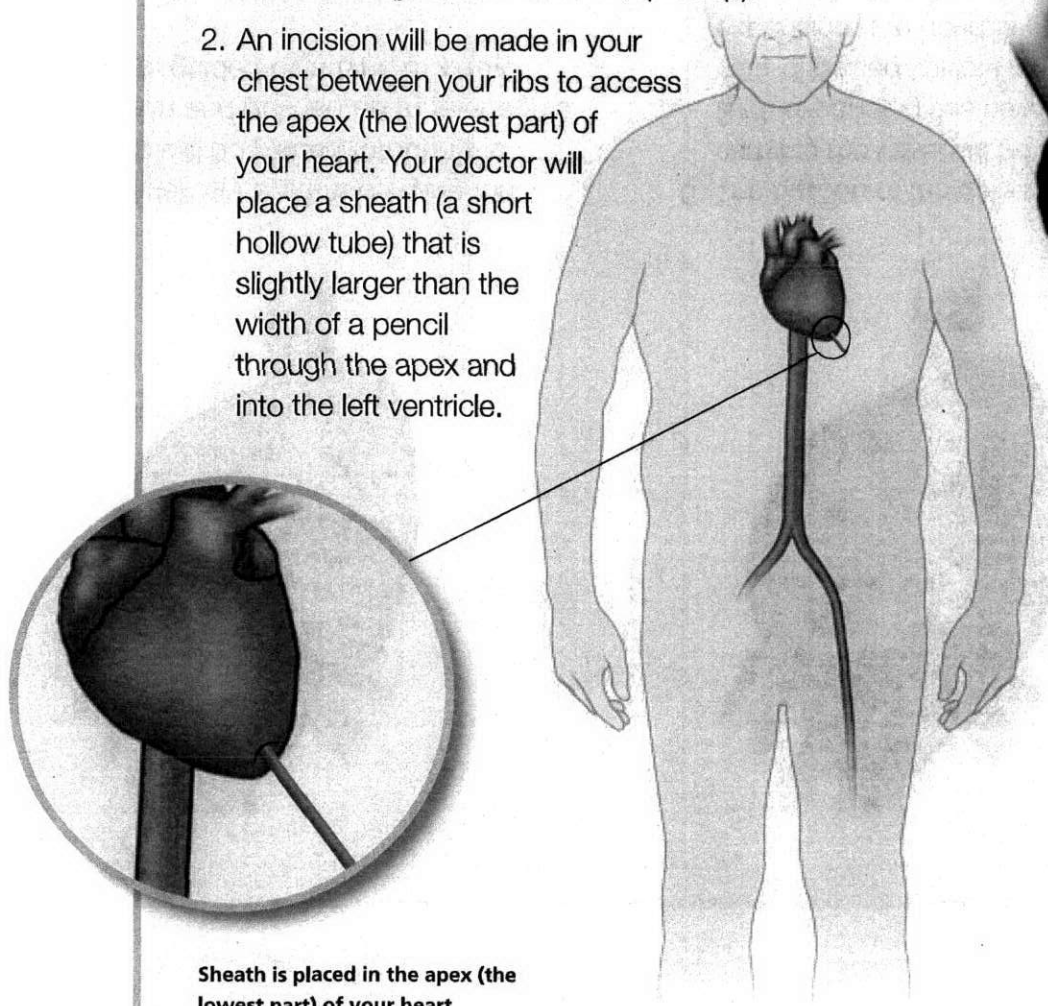
6. The balloon of the delivery system carrying the valve will be inflated with fluid, expanding this new valve within your diseased valve. During valve expansion, the heart is stabilized by temporarily speeding up the heartbeat. The new valve will push the leaflets of your diseased valve aside. The frame of the new valve is very strong and it will use the leaflets of your diseased valve to secure in place. Next, the balloon will be deflated.



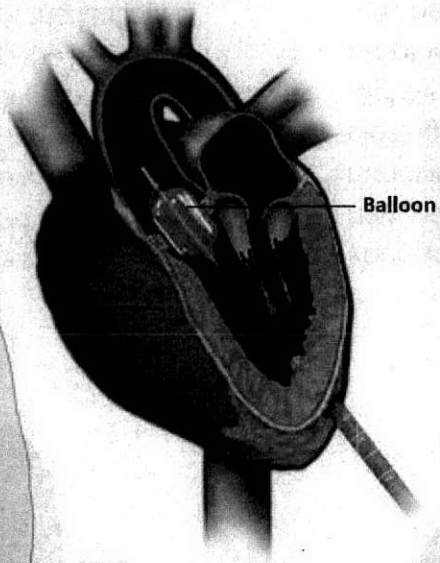
7. Your doctor will make sure that your new valve is working properly before removing the delivery system and closing the incision in your leg (or slightly higher up). If your new valve is not working properly, your doctor may need to do something else which may include open-heart surgery or other additional surgery.

Transapical Procedure *The average time required to perform the transapical TAVR procedure is between 3 and 4 hours.*

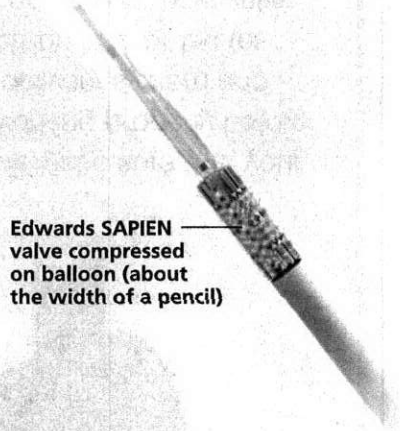
1. You will be placed under general anesthesia (you will be in a deep sleep).
2. An incision will be made in your chest between your ribs to access the apex (the lowest part) of your heart. Your doctor will place a sheath (a short hollow tube) that is slightly larger than the width of a pencil through the apex and into the left ventricle.



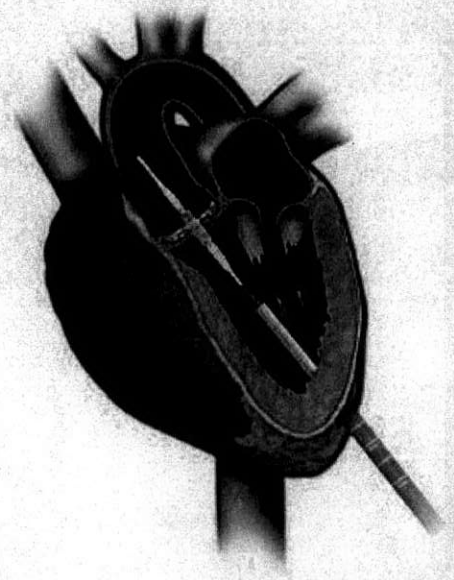
Sheath is placed in the apex (the lowest part) of your heart



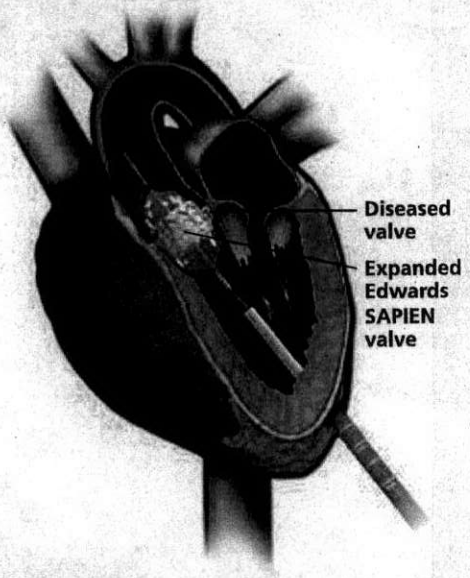
3. Your doctor will take a balloon and put it through the sheath to reach your aortic valve. The balloon will be inflated with fluid to break open your narrowed valve, deflated, and then removed.



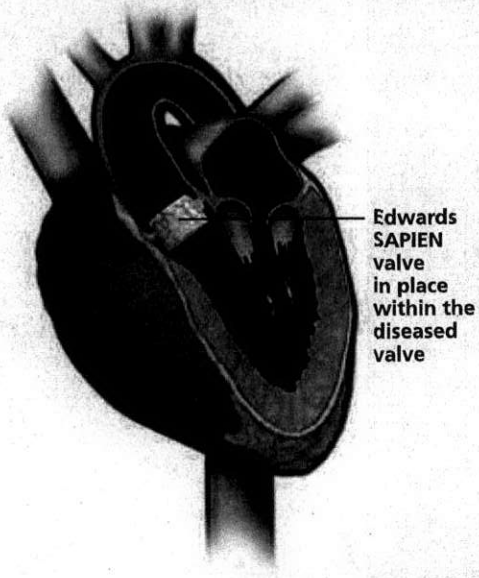
4. The Edwards SAPIEN transcatheter heart valve will be placed on the delivery system (long tube with a balloon on the end), and compressed on the balloon (using a crimper) to make it small enough to fit through the sheath. It will be about the width of a pencil.



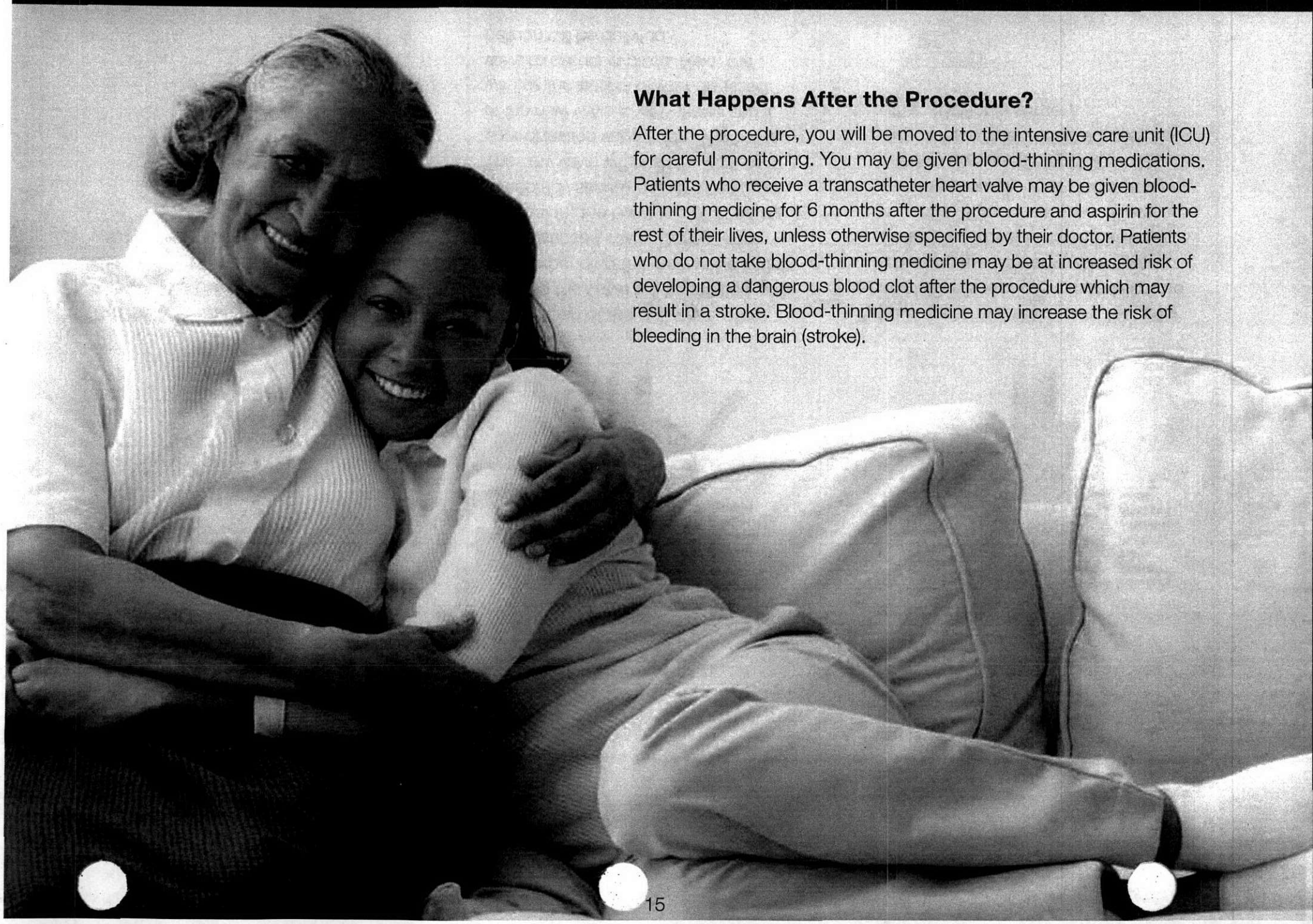
5. The delivery system carrying the valve will be placed through the sheath and pushed up to your aortic valve, guided by a type of X-ray.



6. The balloon of the delivery system carrying the valve will be inflated with fluid, expanding this new valve within your diseased valve. During valve expansion, the heart is stabilized by temporarily speeding up the heartbeat. The new valve will push the leaflets of your diseased valve aside. The frame of the new valve is very strong and it will use the leaflets of your diseased valve to secure in place. Next, the balloon will be deflated.



7. Your doctor will make sure that your new valve is working properly before removing the delivery system and closing the chest incision between your ribs. If your new valve is not working properly, your doctor may need to do something else which may include open-heart surgery or other additional surgery.



What Happens After the Procedure?

After the procedure, you will be moved to the intensive care unit (ICU) for careful monitoring. You may be given blood-thinning medications. Patients who receive a transcatheter heart valve may be given blood-thinning medicine for 6 months after the procedure and aspirin for the rest of their lives, unless otherwise specified by their doctor. Patients who do not take blood-thinning medicine may be at increased risk of developing a dangerous blood clot after the procedure which may result in a stroke. Blood-thinning medicine may increase the risk of bleeding in the brain (stroke).

While in the hospital after the TAVR procedure, the following examinations will be completed:

- Physical exam that includes an exam for stroke
- Chest X-ray
- Blood tests
- Electrocardiography [ECG or EKG] (a test that records your heart's electrical activity)
- Ultrasound of your heart

You will remain in the ICU until your doctor feels you can be transferred to a regular hospital room, where you will continue to be monitored until you leave the hospital.

You should feel better soon after your procedure. Your doctor will give you specific instructions to help you with your recovery, which may include a special diet, exercise, and medicine. It is important to carefully follow your doctor's directions, especially if blood-thinning drugs are prescribed. Your doctor will monitor your medicine and advise you when or if you can stop taking it.

Regular check-ups by your doctor are very important. It is easier for patients with an artificial heart valve to get infections, which could lead to future heart damage. Call or see your doctor whenever you have questions or concerns about your health, especially if you experience any unusual problems such as bleeding, pain, other discomfort, or changes in your overall health.

Even after you have fully recovered from the procedure, your doctor may want to check your progress occasionally. You will need to take any medicine as prescribed and have your heart checked from time to time. Be sure to discuss all your medicine (including over-the-counter medicine) with your doctor, and don't change any dosage unless instructed to, even if you feel better.

Always inform other doctors about your heart valve replacement before any medical or dental procedure. Before undergoing an MRI (magnetic resonance imaging) procedure, always notify the doctor (or medical technician) that you have an implanted heart valve. Failure to do so may result in damage to the valve that could lead to death.

TRANSCATHETER AORTIC VALVE REPLACEMENT CLINICAL DATA

The PARTNER Trial Overview

In the United States, The PARTNER Trial studied the safety and effectiveness of the Edwards SAPIEN transcatheter heart valve in 1,057 patients whose doctors had determined them to be at high risk or too sick to undergo open-heart surgery. The PARTNER Trial was made up of two trial parts – Cohort A (high-risk patients) and Cohort B (inoperable patients). Patient enrollment for the trial was initiated in May 2007 and completed in March 2009.

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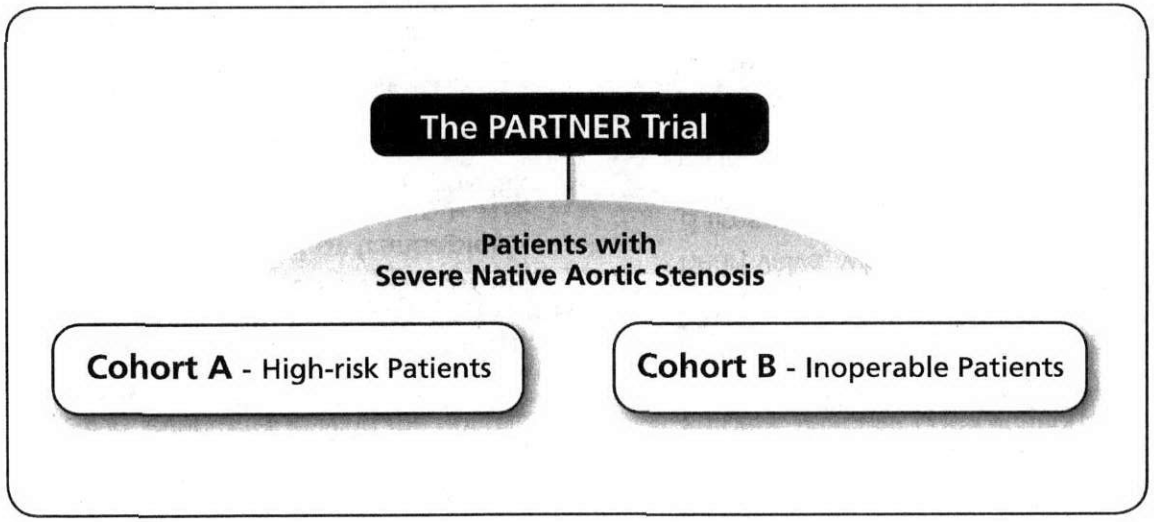
Cohort A (699 patients) evaluated the safety and effectiveness of the Edwards SAPIEN transcatheter heart valve in patients who were deemed by their doctor to be at high risk of death from surgery, but could still undergo an open-chest procedure to replace their aortic valve. These patients are referred to as high-risk patients. Approximately half of the patients in Cohort A were treated with the Edwards SAPIEN transcatheter heart valve (either through the transfemoral or transapical approach) and half were treated with a surgical aortic valve through an open-heart procedure.



Cohort B (358 patients) evaluated the safety and effectiveness of the Edwards SAPIEN transcatheter heart valve in patients who were deemed by their doctor to be too sick to undergo open-heart surgery. These patients are referred to as inoperable patients. Half of the patients in Cohort B were treated with the Edwards SAPIEN transcatheter heart valve (only through the transfemoral approach) and half were treated with standard therapy. Standard therapy included medicine or other procedures that treat aortic stenosis such as balloon aortic valvuloplasty (procedure to stretch the aortic valve opening). The transapical approach was not offered to this patient population as they could not undergo surgery.

Patients in both Cohorts A and B were examined at 30 days, 6 months, and 1 year after the procedure, and will continue to be examined every year for 5 years.

What Are the Most Common Procedural Risks 30 Days After the Procedure?

As with any medical intervention, there is a possibility that complications may occur during or after receiving the Edwards SAPIEN transcatheter heart valve, even after leaving the hospital.

The most serious risks of the TAVR procedure with the Edwards SAPIEN transcatheter heart valve through the transfemoral or transapical approach at 30 days in high-risk patients (Cohort A) include:

- **Death from any cause** – death occurred in 6 out of every 100 patients within 30 days after receiving an Edwards SAPIEN transcatheter heart valve, as compared to 8 out of every 100 patients who received a surgical aortic valve.
- **Stroke** – a condition when blood stops flowing to the brain, which may cause partial or severe disability. Stroke occurred in 5 out of every 100 patients within 30 days after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately 2 times more often than seen in patients who received a surgical aortic valve.
- **Major vascular complications** – a tear or hole in blood vessels or a hematoma (a large blood clot under the skin), which will require another surgery. Vascular complications occurred in 11 out of every 100 patients within 30 days after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately 3 times more often than seen in patients who received a surgical aortic valve.
- **Bleeding event** – a loss of blood that requires 2 or more units of a blood transfusion within the indexed procedure. A bleeding event occurred in 11 out of every 100 patients within 30 days after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately one third less often than seen in patients who received a surgical aortic valve.
- **Aortic insufficiency** – a leakage of blood back through the implanted valve or between the valve and the heart that causes the heart to work harder. Mild aortic insufficiency occurred in 49 out of every 100 patients within 30 days after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately 3 times more often than seen in patients who received a surgical aortic valve. Moderate or severe aortic insufficiency occurred in 17 out of every 100 patients within 30 days after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately 8 times more often than seen in patients who received a surgical aortic valve.

The most serious risks of the TAVR procedure with the Edwards SAPIEN transcatheter heart valve through the transfemoral approach at 30 days in inoperable patients (Cohort B) include:

- **Death from any cause** - death occurred in 5 out of every 100 patients within 30 days after receiving an Edwards SAPIEN transcatheter heart valve, as compared to 3 out of every 100 patients who did not receive a new valve (most of whom had balloon aortic valvuloplasty).

- **Stroke** – a condition when blood stops flowing to the brain, which may cause partial or severe disability. Stroke occurred in 8 out of every 100 patients within 30 days after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately 4 times more often than seen in patients who did not receive a new valve (most of whom had balloon aortic valvuloplasty).
- **Major vascular complications** – a tear or hole in blood vessels or a hematoma (a large blood clot under the skin), which will require another surgery. Major vascular complications occurred in 17 out of every 100 patients within 30 days after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately 9 times more often than seen in patients who did not receive a new valve (most of whom had balloon aortic valvuloplasty).
- **Bleeding event** – a loss of blood that requires 2 or more units of a blood transfusion within the indexed procedure. A bleeding event occurred in 18 out of every 100 patients within 30 days after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately 6 times more often than seen in patients who did not receive a new valve (most of whom had balloon aortic valvuloplasty).
- **Aortic insufficiency** – a leakage of blood back through the implanted valve or between the valve and the heart that causes the heart to work harder. Mild aortic insufficiency occurred in 60 out of every 100 patients within 30 days after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately one and a half times more often than seen in patients who did not receive a new valve (most of whom had balloon aortic valvuloplasty). Moderate or severe aortic insufficiency occurred in 16 out of every 100 patients within 30 days after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately the same as seen in patients who did not receive a new valve (most of whom had balloon aortic valvuloplasty).

What Are the Possible Benefits and Risks 1 Year After the Procedure?

In the high-risk patient group (Cohort A), The PARTNER Trial study results showed that patients who received the Edwards SAPIEN transcatheter heart valve through the transfemoral or transapical approach lived just as long as those patients who received a surgical aortic valve. Approximately 3 out of 4 patients in each group were alive at 1 year after receiving either the Edwards SAPIEN transcatheter heart valve or a surgical aortic valve. Patients who received the Edwards SAPIEN transcatheter heart valve through the transfemoral approach felt better sooner than those patients who received a surgical aortic valve, but the same at 6 months and longer. Patients who received the Edwards SAPIEN transcatheter heart valve through the transapical approach felt worse early on, but the same at 1 year as those patients who received a surgical aortic valve. Patients who received the Edwards SAPIEN transcatheter heart valve had a higher stroke rate than those patients who received a surgical aortic valve.

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The most serious risks of the TAVR procedure with the Edwards SAPIEN transcatheter heart valve through the transfemoral or transapical approach at 1 year in high-risk patients (Cohort A) include:

- **Death from any cause** - death occurred in 24 out of 100 patients after receiving an Edwards SAPIEN transcatheter heart valve. This rate was the same for patients who received a surgical aortic valve.
- **Stroke** – a condition when blood stops flowing to the brain, which may cause partial or severe disability. Stroke occurred in 6 out of every 100 patients within 1 year after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately 2 times more often than seen in patients who received a surgical aortic valve.
- **Major vascular complications** – a tear or hole in blood vessels or a hematoma (a large blood clot under the skin), which will require another procedure. Major vascular complications occurred in 11 out of every 100 patients within 1 year after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately 3 times more often than seen in patients who received a surgical aortic valve.
- **Bleeding event** – a loss of blood that requires 2 or more units of a blood transfusion within the indexed procedure. A bleeding event occurred in 11 out of every 100 patients within 1 year after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately one third less often than seen in patients who received a surgical aortic valve.
- **Aortic insufficiency** – a leakage of blood back through the implanted valve or between the valve and the heart that causes the heart to work harder. Mild aortic insufficiency occurred in 50 out of every 100 patients within 1 year after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately 3 times more often than seen in patients who received a surgical aortic valve. Moderate or severe aortic insufficiency occurred in 23 out of every 100 patients within 1 year after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately 8 times more often than seen in patients who received a surgical aortic valve.

In the inoperable patient group (Cohort B), The PARTNER Trial study results showed that patients who received the Edwards SAPIEN transcatheter heart valve through the transfemoral approach lived longer and felt better, but had a higher stroke rate than those patients who did not receive a new valve (most of whom had balloon aortic valvuloplasty).

- 69 out of every 100 inoperable patients with severe aortic stenosis were alive at 1 year after receiving an Edwards SAPIEN transcatheter heart valve.
- In comparison, only 50 out of every 100 inoperable patients who did not receive an Edwards SAPIEN transcatheter heart valve were alive at 1 year.

- Additionally, the study showed that inoperable patients who received an Edwards SAPIEN transcatheter heart valve had improved heart function and felt much better at 1 year compared to inoperable patients who did not receive a new valve.

The most serious risks of the TAVR procedure with the Edwards SAPIEN transcatheter heart valve through the transfemoral approach at 1 year in inoperable patients (Cohort B) include:

- **Death from any cause** - death occurred in 31 out of 100 patients within 1 year after receiving an Edwards SAPIEN transcatheter heart valve as compared to 50 out of 100 patients who did not receive a new valve (most of whom had balloon aortic valvuloplasty).
- **Stroke** – a condition when blood stops flowing to the brain, which may cause partial or severe disability. Stroke occurred in 11 out of every 100 patients within 1 year after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately 3 times more often than seen in patients who did not receive a new valve (most of whom had balloon aortic valvuloplasty).
- **Major vascular complications** – a tear or hole in blood vessels or a hematoma (a large blood clot under the skin), which will require another procedure. Major vascular complications occurred in 17 out of every 100 patients within 1 year after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately 8 times more often than seen in patients who did not receive a new valve (most of whom had balloon aortic valvuloplasty).
- **Bleeding event** – a loss of blood that requires 2 or more units of a blood transfusion within the indexed procedure. A bleeding event occurred in 17 out of every 100 patients within 1 year after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately 8 times more often than seen in patients who did not receive a new valve (most of whom had balloon aortic valvuloplasty).
- **Aortic insufficiency** – a leakage of blood back through the implanted valve or between the valve and heart that causes the heart to work harder. Mild aortic insufficiency occurred in 59 out of every 100 patients within 1 year after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately one and a half times more often than seen in patients who did not receive a new valve (most of whom had balloon aortic valvuloplasty). Moderate or severe aortic insufficiency occurred in 20 out of every 100 patients within 1 year after receiving an Edwards SAPIEN transcatheter heart valve, which was approximately the same as seen in patients who did not receive a new valve (most of whom had balloon aortic valvuloplasty).

Clinical Risk Tables

The following table is a summary of the clinical risks observed within 1 year in high-risk patients (Cohort A) from The PARTNER Trial. The frequency is shown as the number of patients out of every 100. Risk frequencies for TAVR are broken out by the transfemoral and transapical approach.

Risks Within 1 Year After the TAVR Procedure

	TRANSFEMORAL ARM		TRANSAPICAL ARM	
	Transfemoral TAVR	**Surgical AVR**	**Transapical TAVR**	**Surgical AVR**
Death				
From any cause	21 out of 100 patients	25 out of 100 patients	29 out of 100 patients	25 out of 100 patients
From cardiovascular (heart-related) causes	11 out of 100 patients	11 out of 100 patients	16 out of 100 patients	10 out of 100 patients
Stroke	4 out of 100 patients	1 out of 100 patients	10 out of 100 patients	7 out of 100 patients
Repeat hospitalizations	16 out of 100 patients	15 out of 100 patients	14 out of 100 patients	13 out of 100 patients
Major vascular complications	14 out of 100 patients	3 out of 100 patients	4 out of 100 patients	5 out of 100 patients
Bleeding event	11 out of 100 patients	29 out of 100 patients	8 out of 100 patients	28 out of 100 patients
Aortic insufficiency				
Mild	53 out of 100 patients	18 out of 100 patients	42 out of 100 patients	17 out of 100 patients
Moderate or severe	27 out of 100 patients	3 out of 100 patients	14 out of 100 patients	2 out of 100 patients
New pacemaker (device that can help regulate the heart) implantation	6 out of 100 patients	4 out of 100 patients	6 out of 100 patients	8 out of 100 patients
Kidney failure	5 out of 100 patients	5 out of 100 patients	6 out of 100 patients	9 out of 100 patients

Risks Within 1 Year After the TAVR Procedure (Continued)

	TRANSFEMORAL ARM		TRANSAPICAL ARM	
	Transfemoral TAVR	**Surgical AVR**	**Transapical TAVR**	**Surgical AVR**
Myocardial infarction (heart attack)	0 out of 100 patients	0 out of 100 patients	0 out of 100 patients	0 out of 100 patients
Endocarditis (inflammation or infection of any internal heart structures, including the valves)	1 out of 100 patients	1 out of 100 patients	1 out of 100 patients	1 out of 100 patients

Days Alive Out of Hospital at 1 Year

	TRANSFEMORAL ARM		TRANSAPICAL ARM	
	Transfemoral TAVR	**Surgical AVR**	**Transapical TAVR**	**Surgical AVR**
Days alive out of hospital at 1 year	306 Days	277 Days	280 Days	277 Days

The following tables are a summary of the clinical risks observed within 1 year, and between 1 and 2 years in inoperable patients (Cohort B) from The PARTNER Trial. The frequency is shown as the number of patients out of every 100.

Risks Within 1 Year After the TAVR Procedure

	Transfemoral TAVR	Standard Therapy
Death		
From any cause	31 out of 100 patients	50 out of 100 patients
From cardiovascular (heart-related) causes	20 out of 100 patients	42 out of 100 patients
Stroke	11 out of 100 patients	4 out of 100 patients
Repeat hospitalizations	24 out of 100 patients	44 out of 100 patients
Major vascular complications	17 out of 100 patients	2 out of 100 patients
Bleeding event	17 out of 100 patients	2 out of 100 patients
Aortic insufficiency		
Mild	59 out of 100 patients	43 out of 100 patients
Moderate or severe	20 out of 100 patients	19 out of 100 patients
New pacemaker (device that can help regulate the heart) implantation	4 out of 100 patients	8 out of 100 patients
Kidney failure	2 out of 100 patients	4 out of 100 patients
Myocardial infarction (heart attack)	1 out of 100 patients	1 out of 100 patients
Endocarditis (inflammation or infection of any internal heart structures, including the valves)	1 out of 100 patients	1 out of 100 patients

Days Alive Out of Hospital at 1 Year

	Transfemoral TAVR	Standard Therapy
Days alive out of hospital at 1 year	275 days	247 days

Risks Between 1 and 2 Years After the TAVR Procedure

	Transfemoral TAVR	Standard Therapy
Death		
From any cause	13 out of 100 patients	16 out of 100 patients
From cardiovascular (heart-related) causes	9 out of 100 patients	14 out of 100 patients
Stroke	2 out of 100 patients	0 out of 100 patients
Repeat hospitalizations	9 out of 100 patients	14 out of 100 patients
Major vascular complications	0 out of 100 patients	0 out of 100 patients
Bleeding event	0 out of 100 patients	0 out of 100 patients
Aortic insufficiency		
Mild	13 out of 100 patients	5 out of 100 patients
Moderate or severe	2 out of 100 patients	2 out of 100 patients
New pacemaker (device that can help regulate the heart) implantation	2 out of 100 patients	0 out of 100 patients
Kidney failure	1 out of 100 patients	2 out of 100 patients
Myocardial infarction (heart attack)	1 out of 100 patients	1 out of 100 patients
Endocarditis (inflammation or infection of any internal heart structures, including the valves)	1 out of 100 patients	0 out of 100 patients

Note: Inoperable patients who participated in Cohort B have now been followed out to 2 years. Therefore, these data are available for this patient population.

PRECAUTIONS

- How long your new valve will last is unknown at this time. Regular medical follow-up is essential to evaluate how your valve is performing.
- Transcatheter heart valve patients should stay on blood-thinning medicine for 6 months after the procedure and aspirin for the rest of their lives, unless otherwise specified by their doctor. Patients who do not take blood-thinning medicine may be at increased risk of developing a dangerous blood clot after the procedure which may result in a stroke. Blood-thinning medicine may increase the risk of bleeding in the brain (stroke).
- Transcatheter heart valve patients who are undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of infection.
- The safety of the transcatheter heart valve has not been established in patients who have:
  - A previously implanted artificial aortic heart valve.
  - A ventricle that does not pump efficiently.
  - An enlarged heart.
- The safety and performance of the transcatheter heart valve has not been established for patients who have:
  - An aortic heart valve that is not calcified.
  - An aortic heart valve that only has one or two leaflets.
  - A diseased aortic valve in which the main problem is valve leakage.
  - A previously implanted medical device in any heart valve.
  - A diseased mitral valve that is calcified or leaking.
  - Low white blood cell count, low red blood cell count, or other abnormalities in the blood.
  - Unusual ultrasound images of the heart that could represent abnormalities such as a blood clot.
  - Allergies to blood-thinning medications or dye that is injected during the procedure.
  - An aortic valve that is too small or too big to fit the transcatheter heart valve.
  - Diseased or abnormally shaped vessels leading to the heart.
  - Femoral vessels that are heavily diseased or too small for the delivery device.
  - Aortic valve leaflets with large pieces of calcium that may block the vessels that supply blood to the heart.

WARNINGS

- **The safety and performance of the transcatheter heart valve when placed through the transapical approach has not been established for patients who are not candidates for open-heart surgery.**
- **There is an increased risk of stroke in transcatheter aortic valve replacement procedures, as**

compared to other treatment options for aortic stenosis.

- **There is an increased risk of major blood vessel complications in transcatheter aortic valve replacement procedures, as compared to other treatment options for aortic stenosis.**
- **The artificial valve may not last as long in patients whose bodies process calcium abnormally.**
- **Talk to your doctor if you are allergic to materials such as chromium, nickel, molybdenum, manganese, copper, silicon, and/or polymeric materials.**
- **X-ray is used during the procedure and may cause radiation injury to the skin.**
- **In the trial, the transapical procedure was not offered to and not studied in patients who were appropriate for the transfemoral procedure.**

HOW LONG WILL YOUR NEW VALVE LAST?

How long your new valve will last is unknown at this time. Edwards Lifesciences has tested the valve in the laboratory to replicate 5-year durability. All valves tested for 5-year durability passed the test. The first Edwards transcatheter heart valve was implanted in 2002. However, at this time there is limited long-term information to assess durability beyond 3 years.

The most common reason that a biological valve may fail is a gradual build-up of calcium (mineral deposits). In this situation, the valve may not work properly, which may cause your aortic stenosis to return, and possibly chest pain, shortness of breath, irregular heartbeat, and fatigue. If your stenosis returns or the valve leaks, you may need an additional procedure. Talk to your doctor if you experience any of these symptoms. Regular medical follow-up is essential to evaluate how your valve is performing.

CONTACT INFORMATION

For More Information on the Edwards TAVR Procedure

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(Under Resources)
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(Click on "FOR PATIENTS")

Data on file at Edwards Lifesciences.

CAUTION: Federal (United States) law restricts the Edwards SAPIEN transcatheter heart valve to sale by or on the order of a physician. This device has been approved by the FDA for specific indications for use. See instructions for use for full prescribing information, including indications, contraindications, warnings, precautions and adverse events.

CAUTION: Federal (United States) law restricts the RetroFlex 3 delivery system, RetroFlex 3 introducer sheath set, RetroFlex dilator kit, RetroFlex balloon catheter, Edwards transfemoral balloon catheter, Ascendra balloon catheter, Ascendra introducer sheath set, Ascendra balloon aortic valvuloplasty catheter, crimper and Atrion inflation device to sale by or on the order of a physician. See instructions for use for full prescribing information, including indications, contraindications, warnings, precautions and adverse events.

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